FIRST EPISODE PSYCHOSIS
LOOKING BACKWARDS AND FORWARDS

Ajnakina, Olesya

Awarding institution:
King's College London

FIRST EPISODE PSYCHOSIS: LOOKING BACKWARDS AND FORWARDS

Olesya Ajnakina

Thesis submitted for the degree of Doctor of Philosophy

Institute of Psychiatry, Psychology & Neuroscience

King's College London

University of London

2016

Dedicated to my beloved grandmother, Svetlana. There are no words to begin to describe how much you have inspired me to be the person I am today

(Посвященный моей любимой бабушке, Светлане. Нет никаких слов, чтобы начать описывать, насколько Вы вдохновили меня быть человеком, который я сегодня)

ACKNOWLEDGMENTS

I would like to express my unconditional gratitude to my supervisor Professor Sir Robin M Murray who gave me this chance to pursue a Ph.D in a topic I am so passionate about. I will be internally grateful to him for his encouragements, support and inspiring each day of my work to be full of collaborations and new ideas.

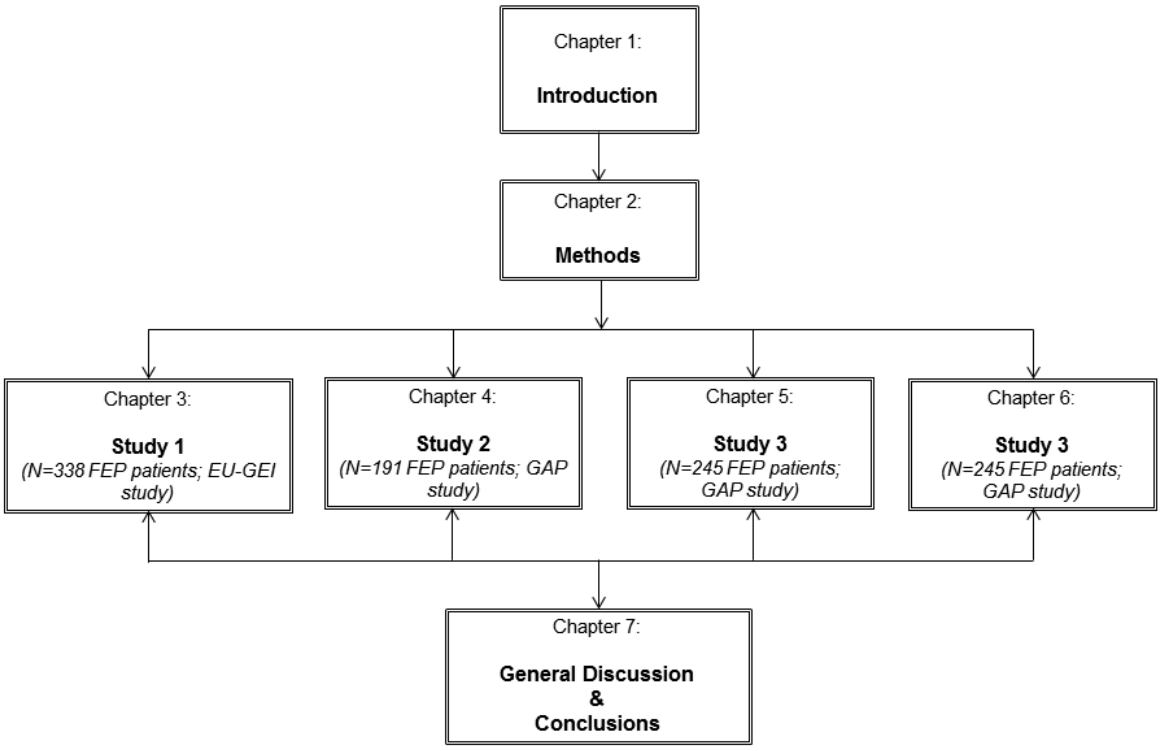
I would like to express special gratitude to Professor Anthony David for all his support and encouragement with my research, and generally believing in me and my skills. Dr Helen Fisher, you have been the constant source of support and friendship to me ever since I came to KCL as a novice student; I will be forever grateful to you for it. Special thanks to Averil Baxter for her support with day-to-day tasks and a laughter that we shared together for over three years. Dr Marta Di Forti's kindness and support have especially touched my heart. I am grateful to Dr John Lally for his patience and willingness to collaborate with me on different projects. My gratitude goes to Dr James MacCabe for his kind assistance in writing up this thesis.

I would now like to thank my family who believed in my choice of pursuing a career in research and supported me all along. My grandmother has been a source of energy, inspiration and emotional support. Especially I thank my wonderful sister for her patience. Undoubtedly, it is their unconditioned love and trust that made this thesis possible. And last but not least I would like to say thank you to Lee Goodwin for being a csource of light and support throughout my write-up.

Of course, there are many others who have helped me with my Ph.D thesis in different ways; though I did not mention you all by name, please know I am grateful to you all for everything you have done for me from the moment I began my PhD thesis to the last day of submission.

ORGANIZATION OF THE THESIS

This Thesis comprises a total of seven chapters. Chapter 1 is introductory including aims and hypotheses. Chapter 2 describes the methods and statistical analyses. The experimental part of the Thesis is presented in Chapters 3-6. Each of these chapters has a brief introduction, followed by the specific methods, the findings, and conclusions. Finally, in Chapter 7 a general discussion of the findings is presented.



ABSTRACT

Introduction Psychotic disorders are known for their wide variability in clinical and social outcomes beginning from illness onset and throughout their course. Our current lack of understanding of the origins for this heterogeneity is further compounded by dearth in knowledge on how patients come to the attention of mental health services and methodological incongruity across different studies. Employing samples of first episode psychosis (FEP) patients, the aims of this thesis were to: 1) look back on the pathways to care patients used to enter mental health services and the use of prodromal services in South London; and 2) examine trajectories of the psychotic disorders and potential predictors of their longitudinal outcomes.

Methods Two large samples of patients with FEP (i.e., GAP and EU-GEI) were utilised in this thesis. For the study 1, information on pathways to care undertaken prior to coming to generic services for FEP was extracted from the Biomedical Research Centre (BRC) Case Register Interactive Search (CRIS) system. For studies 2, 3 and 4, using electronic clinical records, extensive information in three domains-clinical, social and service uses-was collated over 4-5 years after contact with mental health services.

Results Only a small fraction of individuals (4.1%) who present with FEP to the main secondary mental health provider have previously been in contact with prodromal services and made a subsequent transition to psychotic disorder; 77% this sub-group of patients entered their pathway to care via referral from General Practice or other health professional. In contrast, 45% of FEP group without prior contact with the prodromal services made first contact with mental health services via emergency services and 18% of this group were referred by the criminal justice system. Further, combining the baseline schizophrenia diagnosis with five symptom dimensions (i.e., positive, negative, excited, disorganised/concrete and depressed dimensions) generated the best model fit for predicting time to first remission.

During the 5-year follow up after first contact with mental health services, a higher proportion of Black African and Black Caribbean ethnicity had compulsory re-admissions and instances of police involvement during an admission to a psychiatric unit compared with White British ethnic group. Patients of Black African and Black Caribbean ethnicity did not differ from White British ethnic group in overall functional disability and illness severity, or frequency of remission or recovery during the follow up period. However, patients of Black ethnicity become increasing socially excluded as their illness progress.

In a sample of first-episode schizophrenia spectrum patients, 35% of the sample met the criteria for treatment resistance (TR) at the end of the first 5 years of follow up. Of these TR patients, 70% of these were treatment resistant from illness onset. Those who subsequently developed TR were more likely to have an early illness onset (<20 years) compared to those with non-TR. The relationship between an early age of onset (<20 years) and TR was specific to patients of Black ethnicity and patients of male gender.

Conclusions Very few of those who come to FEP services come after being seen for an at-risk-mental state by prodromal services suggesting that the scope for reducing or delaying onset of psychosis by this means may still be limited. My results indicate that supplementing the baseline categorical schizophrenia diagnosis with ratings on five symptom dimensions improves the prediction of delayed treatment response as measured by time to first remission. Further, the longitudinal trajectory of psychosis in patients of Black ethnicity did not show greater clinical or functional deterioration than white patients. However, their course remains characterised by more compulsion, and longer periods of admission. Finally, I showed that for the majority of the TR group, lack of response to antipsychotic treatment is present from illness onset, necessitating a consideration for an earlier use of clozapine.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVATIONS

Abbreviation	Interpretations
AESOP	Aetiology and Ethnicity in Schizophrenia and Other Psychoses
AFT	Accelerated failure time
ARMS	At Risk Mental State
AUDIT	Alcohol Use Disorders Identification Test
BIC	Bayesian Information Criterion
BRC	Biomedical Research Centre
CEQ	Cannabis Experience Questionnaire
CFA	Confirmatory factor analysis
CGI	Clinical Global Impression Scale
CRIS	Case Register Interactive Search
DNA	Deoxyribonucleic acid
DSM	American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders
DUP	Duration of Untreated Psychosis
E-TR	Early-Resistance
EPCR	Electronic psychiatric clinical records
EU-GEI	European network of national schizophrenia networks studying Gene-Environment Interaction
FEP	First Episode Psychosis
FES	First epidote schizophrenia
GAF	Global Assessment of Functioning
GAP	Genetics and Psychosis
GFI	Goodness-of-Fit Index
GP	General Practitioner
GRO	General Register Office
HR	Hazard Ratio
ICD	World Health Organization's International Statistical Classification of Diseases and Related Health Problems
IQ	Intelligence Quotient
IQR	25th and 75th Percentiles range
IRR	Incidence Rate Ratio
L-TR	Late-Resistance
LCS	Life Chart Schedule
MHA	Mental Health Act
ML	Machine learning
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
non-TR	Non-Treatment Resistance
OASIS	Outreach and Support in South London Service
ONS	Office for National Statistics
OPCRIT	Operational Criteria Checklists
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale
PLR	Penalised logistic regression
PRS-SZ	polygenic risk score for schizophrenia
PSQ	Psychosis Screening Questionnaire
RCT	Randomised controlled trials s
RDC	Research Diagnostic Criteria

RMSEA	Root Mean Square Error of Approximation
RNA	Incidence Rate Ratio
RSWG	Remission in Schizophrenia Working Group
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SLAM	South London and Maudsley National Health Service Foundation Mental Health Trust
SPSS	Statistical Package for the Social Sciences
SRMR	Standardised Root Mean Square Residual
STATA	Data Analysis and Statistical Software
SZ	Schizophrenia
TR	Treatment Resistance
TRS	Treatment resistant schizophrenia
WHO	World health organisation

CHAPTER 1 INTRODUCTION

1.1. Introduction

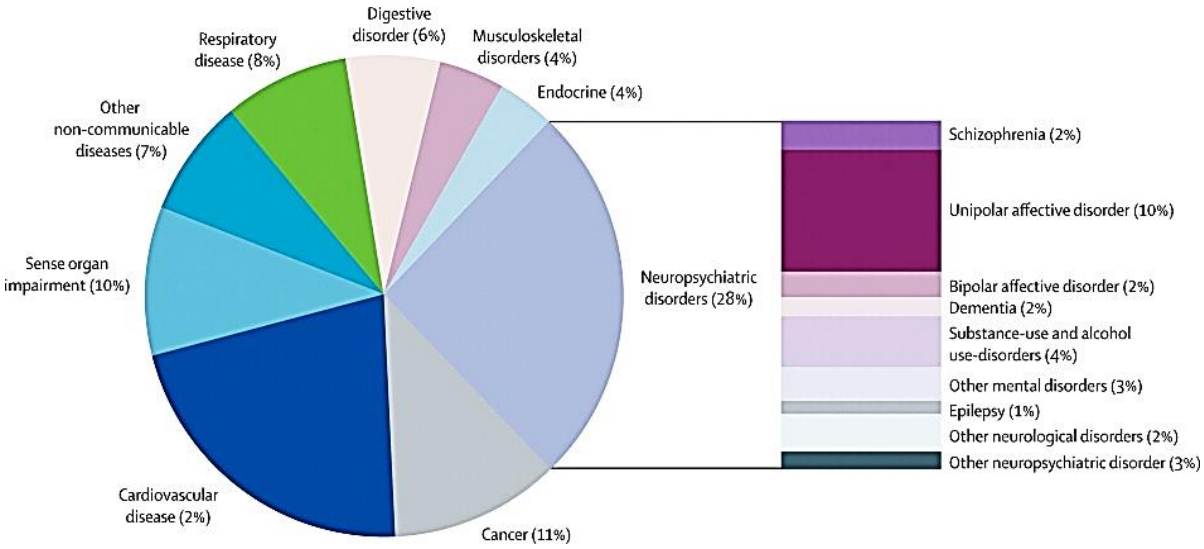
Over the past century, research into causes and treatment of many neuropsychiatric diseases has been marked with important successes. For example, such illnesses as pellagra and neurosyphilis, that have prominent underlying psychiatric manifestations, are now rare in many parts of the world[1]. These triumphs stand in sharp contrast to decades of frustration in elucidating the aetiology of psychotic disorders [1].

1.2. Overview of "Psychosis"

The term "Psychosis" indicates a mental state characterised by a set of "psychotic" symptoms which can be classified as positive and negative. Positive symptoms involve impaired reality testing and may encompass strong false beliefs held against evidence of the contrary; these are also referred to as "delusions". Abnormal perceptions, including illusions, in any of the five sensory modalities, are known as hallucinations [2]. Negative symptoms include emotional and social withdrawal, loss of motivation, poverty of speech, inability to experience pleasure and apathy [3]. The pathophysiology of negative symptoms is still poorly understood, which may partially explain their resistance to the currently available treatments[4]. Depending on severity, all psychotic symptoms can lead to unusual or bizarre behaviours, impaired social interaction and poor self-care ultimately causing a decline in level of functioning [4].

As shown in the **Figure 1**, not surprisingly, psychotic disorders as a whole, and schizophrenia (SZ) in particular, are leading causes of disability worldwide [5]. They are associated with a tremendous personal, social and economic burden [6] most of which is due to the functional disabilities [7]. Indeed, patients affected with SZ have difficulties in obtaining or maintaining a job, having enjoyable social or interpersonal relationships, living independently and for some patients taking care of their basic daily needs becomes increasingly challenging.

Figure 1. *Contribution by different non-communicable diseases to disability-adjusted life-years worldwide in 2005*



This figure is adopted from Prince *et al* (2007)[5]

1.3. Diagnostic of Psychotic Disorders

The current classification systems of psychotic disorders, such as the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, 10th Edition or ICD-10 for short [8] and American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, or DSM-IV for short [9], are derived from the work of Kraepelin (1919), Bleuler (1911) and Schneider (1959) [10,4]. Kraepelin described Dementia Praecox (this concept will gradually become known as Schizophrenia) as a disorder characterised by a chronic and deteriorating course and rapid cognitive disintegration[10]. He considered it a unique disease entity with a single aetiology and defined pathology [4]. Bleuler rechristened the disorder as SZ and deemed its essence was not delusions and hallucinations but rather a disintegration of different psychic functions. These in turn were believed to lead to its fundamental symptoms of loosening of association, blunt or incongruous affect, ambivalence and autism (*Bleuler's 4 As*) which were present in all cases [10]. Schneider (1959) defined 11 first-rank symptoms which he believed to be pathognomonic [2]-these symptoms are now considered as positive symptoms of SZ [4].

While attempting to identify 'true' SZ from the pseudo-schizophrenia or schizophreniform psychoses by the 1960s the USA adopted the Bleulerian perspective when diagnosing patients with SZ; whereas, the Kraepelinian and Schneiderian concepts prevailed in the rest of the world. These differences led to wide discrepancies in rates of diagnosing SZ between the USA and the rest of the world. However, the American concept of SZ was narrowed with the introduction of DSM-III. Consequently, now according to the ICD-10 classification system [8], a diagnosis of SZ is given if psychotic symptoms continuously persisted for one month or longer; whereas, the DSM-IV requires a minimum duration of six months [9].

As for diagnoses of other psychotic disorders, an ICD-10 and DSM-IV diagnosis of Schizoaffective disorder (SAD) is reached when the criteria for both a mood episode and SZ have been reported by patients for two weeks or longer. Psychotic symptoms which occur only in the context of a mood disorder are classified as Affective Disorders which are, according to the ICD-10, further subdivided into 1) Mania with psychotic symptoms; 2) Bipolar Affective Disorder, manic with psychotic symptoms; 3) Bipolar Affective Disorder, Severe Depression with psychotic symptoms; 4) Severe Depressive Episode with psychotic symptoms; and 5) Recurrent Depressive Disorder, severe with psychotic symptoms. The reclassification of the affective disorders according to the DSM-IV is as follows: 1) Bipolar-I Disorder, most recent episode (i.e., Manic or Mixed or Depressive, all severe with psychotic features); 2) Major Depressive Disorder, single episode, severe with psychotic features: 3) Major Depressive Disorder, recurrent, severe with psychotic features.

1.4. Symptom Dimensions[1]

The supporters of the dimensional approach to psychotic disorders argue that the currently endorsed nosologies are founded on the common practice of grouping a diverse set of patients into a single diagnostic category [11]. Although a subdivision of SZ into positive and negative syndromes was believed to enhance its diagnostic validity [12, 13], further investigations have consistently demonstrated that this dichotomy was an oversimplification [12-14] with important implications for research, diagnostics and treatment [15]. Instead, it is postulated that the phenomenology of psychotic disorders may be better conceptualised by a number of symptom dimensions [13] (although the ideal number and features of these

[1] This section was published in David, A S. and Ajnakina, O. (2016). Psychosis as a continuous phenotype in the general population: The thin line between normality and pathology. *World Psychiatry*, 15(2):129-30. doi: 10.1002/wps.20327.

dimensions is not confirmed), as this approach acknowledges an existence of distinct subgroups of symptoms [16, 17] that are unique in their clinical presentation and trajectory [13].

The concept of the dimensional approach offers a number of unique opportunities. Firstly, recognising the psychosis phenotype as a gradual infusion of quantitative traits into clinical syndromes provides an elegant explanation for variation in the degree of severity of psychotic symptoms observed across different patients. Secondly, the dimensional approach implies that it is not restricted to any specific psychotic disorder but rather represents a continuous expression across the psychosis spectrum. This may explain the overlap in psychopathological presentation observed across mental disorders and therefore may provide a foundation for cross-disorder analyses. The latter in turn would tackle the indistinctness of current diagnostic categories that are marked by a lack of clear boundaries between themselves and with normality [18]. Although the idea of considering psychopathology in terms of psychosis dimensions may still be perceived as agnostic with respect to traditional diagnostic systems, using these two approaches in combination may allow for a more accurate classification of affected individuals [19, 20]. The dimensional approach may also have important advantages in scientific research. In research carried out by my group employing psychosis dimensions, a degree of specificity was found in the relationships between different types of childhood trauma and psychosis symptom dimensions in adulthood suggesting that distinct pathways may be involved in the relationship between the childhood trauma and psychosis [21]. Similarly, Jones *et al* [22] have demonstrated the importance of different dimensions in exploring how an increased genetic risk for SZ expresses itself during early teens among the general public. Certainly, building on these findings, future studies may shed some light on the pathways between the genetic liability for SZ and phenotypical expression of this illness in childhood, adolescence and throughout adulthood.

1.4.1. Symptom dimensions: Wallwork/Fortgang'sfive factor model

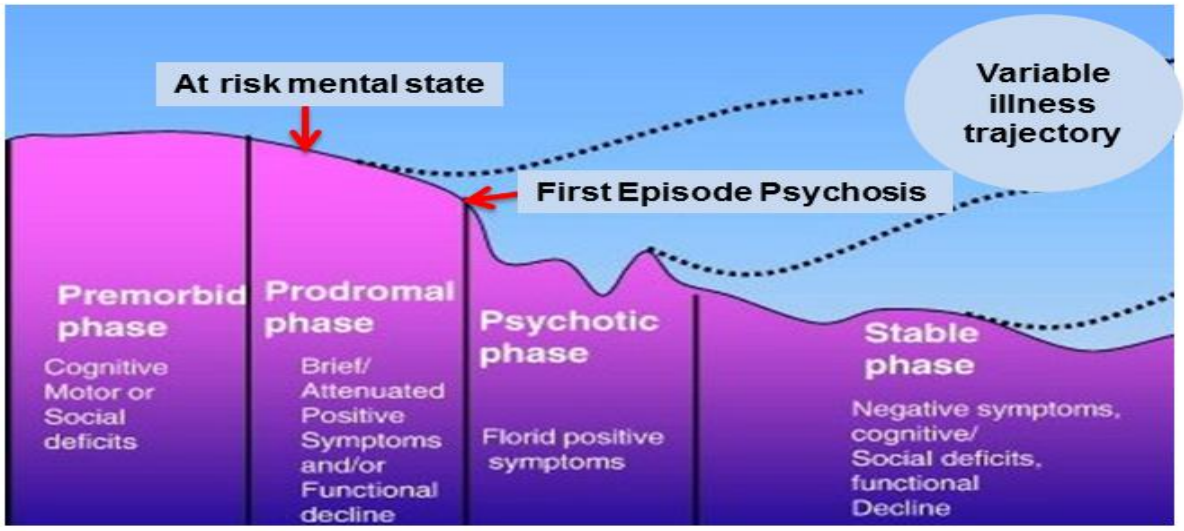
To-date a number of multidimensional models with five factors have been reported [14, 23-25]. Based on previous work, Wallwork *et al* [26] derived a consensus five factor model of psychosis that comprised of the positive (e.g., delusions, hallucinatory behaviour), negative (e.g., blunted affect, emotional withdrawal), disorganised/concrete (e.g., conceptual disorganisation, difficulty in abstract thinking), excited (e.g., excitement, hostility) and depressed (e.g., depression, guilt feeling) dimensions. Langeveld's *et al* [27] further

comparative analyses have highlighted that the Wallwork/Fortgang's model [26] was the most robust model for exploring the symptom profiles in patients who have not been affected by factors associated with a long-term course of illness. Therefore, I will utilise this model in my analysis (Chapter 4, Study 2, pages93-113)

1.5. Onset and course

As **Figure 2** illustrates, SZ is characterised by a sequential trajectory that involves a *premorbid phase* with subtle and nonspecific cognitive, motor and/or social dysfunction, a *prodromal phase* characterised by attenuated positive symptoms or basic symptoms and decline in functioning, and the *first psychotic episode* (FEP) indicating formal onset of the psychotic disorders. In this PhD thesis, I will focus on the *prodromal* and *FEP* phases.

Figure 2. *Onset and course of Schizophrenia: Premorbid phase, Prodromal phase and onset of First psychotic episode*

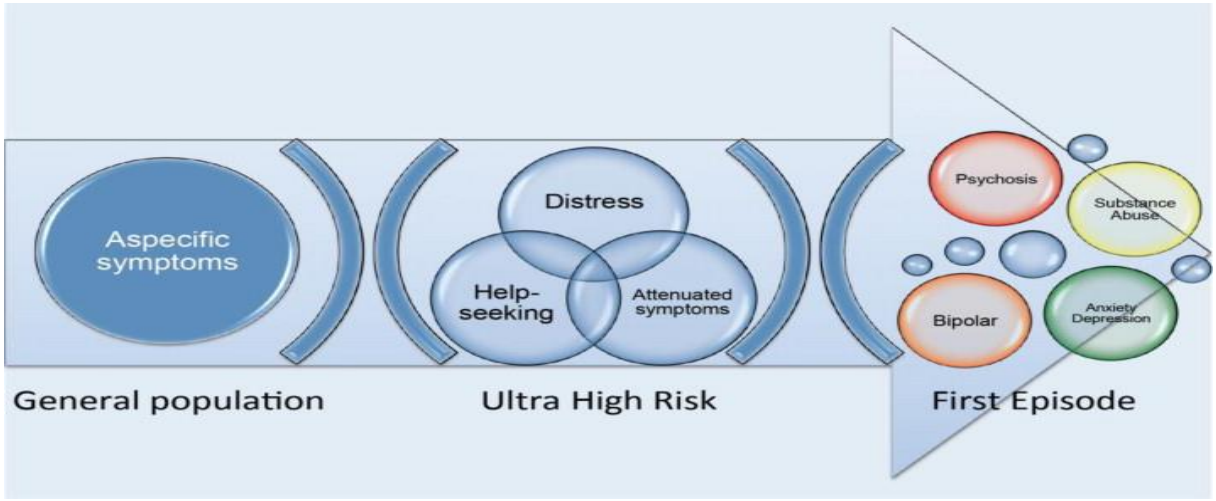


This figure is adopted from Tandon *et al*. (2004)

1.5.1. Prodromal Phase

As outlined in **Figure 3**, the FEP is often (but not always) proceeded by the At Risk Mental State (ARMS) (this phase is also referred to as Ultra High Risk) [28]. The ARMS is characterised by either 'attenuated' psychotic symptoms the severity of which do not warrant the diagnosis of a clinically defined psychotic disorder, full yet brief and self-limiting psychotic symptoms, or a significant decrease in functioning in the context of a genetic risk for SZ [29, 30]. It is further defined by subtle subjective disturbances of cognitive processes, thinking, perception, mood, affect and behaviour. The ARMS phase was initially shown to associate with up to a 30-45% chance of developing a full-blown psychotic disorder in the following 24 months [31]; this risk further increased to 54% within 31 months [28, 30, 32]. However, more recent studies have reported a lower transition rate[33]. Identification of ARMS individuals provides a unique opportunity to reduce the duration of untreated psychosis (DUP), which in turn may improve the overall prognosis of psychosis [34], deferring or decreasing transition to psychotic disorders and reducing the financial or emotional burdens associated with these disorders [28, 34, 35]. This recognition has ignited new interest in prodromal services for those individuals who are perceived to be at high risk for developing psychosis.

Figure 3. *Depicting that the vulnerability to psychosis distributed on a continuum in the general population*



This figure is adopted from Fusar-Poli *et al* (2013) [28].

1.5.2. ARMS and Pathways to Care

The ARMS services in South London (UK) provide comprehensive care to young individuals age 14-35 years old meeting criteria for the ARMS [28, 30, 36, 37]. Having established close links with primary care providers and non-health related community services, such as school counsellors and emergency and criminal justice services, the ARMS services claim to have created an accessible and acceptable service for help-seeking young people who are at risk for psychosis [28, 38]. Although up to 8% of the general population meet the criteria for the ARMS [39], the proportion of individuals with FEP who access the mental health care via the ARMS services is still unknown. Current knowledge of pathways to care for those at high risk of psychosis remains relatively sparse [40]. It is also unclear whether pathways to care in prodromal cases differ from those patients who present to conventional mental health services for FEP. A better understanding of how different groups interact with healthcare systems may allow us to more effectively target interventions aimed at reducing DUP and improve pathways to care [41]. To access the prodromal services, however, patients are expected to demonstrate active help-seeking. This condition may introduce a bias whereby those individuals who are at high risk for transition and who presented to the prodromal teams may be unrepresentative of the overall population of people with ARMS. Additionally, earlier studies showed that a high proportion of those referred to prodromal services were already in a frank first episode at the time of the contact [28]. Yet, it is not known whether this subgroup of FEP patients constitutes the same subgroup of patients as those FEP cases who did not have prior contact with prodromal services, or whether prodromal teams perform a useful function in detecting FEP patients who otherwise might not be referred to regular FEP care.

1.5.3. First psychotic episode (FEP): Definitions and challenges

The FEP studies recruit all individuals presenting to mental health teams for the first time with psychotic symptoms over a specified period. Defining the onset of FEP can however be challenging due to substantial variations in the definition of what constitutes an onset of the illness (i.e., first sign of mental disturbance, positive symptom, evidence of social dysfunction, clinical contact or hospitalisation). A few studies applied the first hospital admissions as a selection criterion for FEP[42-48]. However, this criterion for FEP is associated with a number of important limitations. By recruiting patients on the first admission, these studies potentially omit about 10-20% of affected individuals who will never be admitted to

psychiatric wards [49, 50]. This selection criterion could also lead to female patients being under-represented in these studies as women tend to have a less severe illness course and may therefore be more often treated on an outpatient basis [49]. Additionally, applying the first hospital admission as a selection criterion for FEP may bias recruitment in favour of patients with a more severe presentation and poorer outcomes [50]. Further, there is a large discrepancy in the age limits in inclusion criteria of potential research participants. A few studies limited their inclusion criteria to patients aged 15-54 years [48, 51-55]; whereas others indicated a lower age limit (i.e., 12-13 years old) [44, 56, 57]. An arbitrary age cut-offs may jeopardise generalisability of the findings [58]. Studies of unselected samples of incident cases with all psychotic disorders remain relatively rare.

1.6. Psychosis and Ethnicity

Psychiatric epidemiology has consistently demonstrated elevated rates of psychotic disorders among those of Black ethnicity residing in the UK [59-61]. This contrasts with lower rates of psychosis found among Irish people and conflicting results in Asian populations [62, 63]. With a significant influx of immigrants of African and Caribbean descent, it was originally postulated that those who tended to migrate from their native country were already vulnerable to developing psychosis [64, 65]. This theory however did not stand the test of time as the rates pf reported psychosis remained high among the generations born in the UK [66, 67]. Subsequently, it was suggested that individuals of Black ethnicity were more likely to be misdiagnosed with psychosis [59], others blamed a stronger genetic predisposition to this disorder [67, 68]. Without reliable evidence being produced [66, 69], these theories have lost their prominence. Further research has shown elevated rates of psychosis occur among those of lower social class [70, 71]. This relationship is not a simple consequence of geographic drift or segregation [72] but rather an area marked by social deprivations in itself may be a risk factor for psychosis [53]. The evidence suggests that a majority of Black ethnic minorities in the UK live within a toxic environment characterised by high levels of deprivation, unemployment and social exclusion [73]. However, despite the importance of investigating the potential causes for this relationship between the ethnicity and the elevated risk for psychosis, research in this area is marked by dearth of studies, methodological heterogeneity and flaws [74].

1.7. The importance of follow up studies

The FEP studies recruit all individuals presenting for the first time with psychotic symptoms over a specified period and mental health teams, and then follow them over a specified period. The follow up studies have a two-fold purpose [49]. First, this study design aims to identify the patterns of variability in the course and outcomes of the illness; this is referred to as *natural-history studies* [49]. Second, this study design can be used to identify factors that may either modify outcomes or identify the risks for poorer outcomes (*prediction-of-outcome studies*) [49]. Such studies reflect the continuous interplay between an individual, the illness and the environment [49], they are important for the research and ultimately clinical practice. For example, they may be able to deepen our current understanding of prognostic factors, or identity factors that are linked to poorer treatment response. This in turn will help identify specific patient populations that may be less or more likely to respond to a treatment, and as such will help clinicians select treatments that are more likely to succeed. So far a number of longitudinal studies have been conducted exploring course and outcomes in patients with FEP and I will present them in **Tables 1** and **3** (pages 29 and 49).

1.8. Why is it important to use a FEP sample in this study design?

Studies that examine the longitudinal outcomes of psychotic disorders measure dynamic and multidimensional relationships between the patients and treatments. Therefore, it is important to focus on a sample of patients whose symptomatology is not affected by chronicity of illness or prolonged medication use[25]. The sample recruited at the time when the first episode occurred represents a patient population that clinicians see in everyday clinical practice. This type of sample stands in sharp contrast to patients with an established diagnosis of SZ who represent the severe end of the psychosis phenotype[75]. FEP patients have a common starting point in their illness course, and are thus more suited to studying the variability and determinants of course and outcome over a period of time [74, 76].

1.9. Definition of Outcomes

The ‘Outcome’ refers to the longitudinal trajectory of illness. The outcome studies generally include a baseline assessment (referring to the assessments conducted at study entry) and follow-up assessments that can take place at any point during the follow up period. It is

important to note that this definition of the outcome does not imply that the illness process has an endpoint[49]. Instead, it indicates that an end point in any given study design is the end of the follow up period[49]. There are no limitations on what may constitute an outcome, as an outcome can be measured in different dimensions, such as cognitive or psychosocial function, as well as in clinical terms e.g. number of hospitalisations, remission and recovery.

1.10. Longitudinal outcomes in FEP patients: Systematic literature review

I have conducted a systematic review of all studies that were published on recovery and remission as well as service utilisation and social outcomes, in accord with the Meta-analysis of Observational Studies in Epidemiology guidelines [77] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses standard [78]. The main aim of the systematic review was to provide a comprehensive overview of all available studies conducted on clinical outcomes (i.e., remission and recovery), social outcomes (i.e., living arrangements, employment and relationship status) and service utilization over illness course after onset of FEP, and whether the reported results across studies were consistent; notably I did not assess the published studies in terms of their methodological robustness and importance of their findings in this review as this was not my aim.

1.10.1. Inclusion criteria for the studies

I included studies of longitudinal observational design both retrospective and prospective studies in patients with FEP (including FES and first episode affective psychosis) without upper or lower age limit who fulfilled the following criteria:

I. Reporting remission rates recovery rates, in people with a FEP irrespective of clinical setting (i.e., inpatient, outpatient or mixed).
II. Individuals with FEP who were making their first treatment contact or in their first admission for FEP
III. Using a specified standardised diagnostic system (e.g. ICD, versions 8,9 and 10), DSM (versions III and IV), Bleuler's diagnostic criteria, Kraepelin & Feighner's diagnostic criteria, Royal Park Multidiagnostic Instrument for Psychosis, and the Research Diagnostic Criteria (RDC)

IV. Studies that reported information on social outcomes such as employment, living arrangement and relationship status
V. Studies that reported information on service use such as number of total hospital re-admissions and total length of inpatients stay during the follow up period
VI. English language articles published in a peer reviewed journal from inception to July 2016
VII. A prospective follow up of >12 months

1.10.2. Exclusion criteria

I excluded from this systematic review all studies that were:

I. Randomised controlled trials (RCTs); although these might have reported rates of remission and/recovery, they did not represent a naturalistic progression of the illness due to their non-naturalistic design
II. Studies that examined efficiency of clinical treatments such as psychotherapies or antipsychotic medications
III. Studies that did not include people with psychosis
IV. Studies that were not FEP cohorts
V. Studies of organic psychosis

1.10.3. Search criteria

I searched PubMed, Medline, and Scopus without language restrictions from database inception. Key words used were “first episode psychosis” OR “early episode psychosis” OR “schizophrenia” OR “schiz*” AND “remission” OR “recovery” AND “outcome” OR “follow-up” OR “hospital admission” OR “treatment” OR “social outcomes”.

1.10.4. Results of systematic literature review

Comprehensive descriptions of all identified studies that examined clinical outcomes are presented in **Table 1** and all the longitudinal studies that examined services use and social outcomes in FEP cases are presented in **Table 3**. I will give an overview of the main findings

for each outcome below in the subsequent sections. All identified studies are listed in **Tables 1** and **3** in the alphabetical order; for every identified study I outlined study design sample characteristics and proportion of patients who met criteria for each outcome (i.e., remission or recovery, etc.) and rates of patients who were successfully followed up. In **Table 1**, I aimed to provide definitions of recovery and remission used for comparison across the studies; if the outcome was examined, but a definitions used were not stated in the original article “not stated” phrase is used in the table.

Table 1 *A review of previous longitudinal studies examining social and clinical outcomes, and services use in a sample of patients with first episode psychosis*

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Addington & Addington [79] 2008 Canada	FE non-Affective psychosis	3	240	61.3	147	82	18	24.5					36.7	RSWG 2005 criteria
Alaghband-Rad *et al*[80] 2006 Iran	FEP	2	54	90.7	49	46.3	53.7	24.2					77.8	Asymptomatic for 4 weeks or longer
Albert *et al* [81] 2011 Denmark	FES spectrum	5	468	46.6	54.4 872	56.1	43.9	26	29		15.7	Remission of both negative and psychotic symptoms, no hospitalisations and not living in a supported housing facility, GAF score >60 and employed (or studying) during the past 2 years.		RSWG 2005 criteria
Alvarez-Jimenez *et al* [82] 2012 Australia	FES spectrum	7.5	307	68.1	209	73.2	26.8	21.9	79.9	9.6	26	Symptomatic remission (as adopted from Andreassen *et al*, 2005) with the exception of 6 month duration component and vocational functioning defined as independent living and peer contact more than once per week. No duration was provided		
Austin *et al*[83] 2013 Denmark	FEP	10	496	61.3	304	55	45	26.2			30	Remission of both negative and positive symptoms, no psychiatric admissions to hospital or living in supported accommodation for the past two years. Additionally, engaged in work or study and a GAF score >60 at the end of follow up	64	Symptom remission was defined as the display of minimal–mild positive and negative symptoms on the global scores for SAPS and SANS for at least 6 months
Benoit *et al* [84] 2014 Canada	FEP Non-Affective psychosis	1			70	75.7	24.3	23					24.3	RSWG 2005 criteria

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Berg *et al* [85] 1983 Sweden	FEP	23.5	22	90.9	20	100	0	26	85	30	80	Not stated		
Bernahardt&Gottlieb [86] 1940 USA	Hebephrenia	5	100	93	93	49	51			94	8.6	Patients no longer presented any of the SZ processes, once more entered into a successful social relationship, exhibited wholesome interest in life and ability to deal with its problems		
Bertelsen *et al* [87] 2009 Denmark		5	547	48.4	265	65	35	26	53		18	Symptomatic remission (as adopted from Andreassen *et al*, 2005), living independently, working and GAF>59 score. Duration component not stated		
Bromet et al[88] 2005 USA	Bipolar disorder	4	123	86.2	106	47.2	52.8	29.5					83.7	Patient did not meet DSM-IV criteria for a mood disorder for 8 weeks or longer
Carlson *et al* [89] 2000 USA	bipolar disorder with psychotic mania	2			53	69.6	30.4	18.3					74.4	
Chang *et al* [90] 2012 Hong Kong	FEP	3	700	77	539	51.6	48.4	21	28.6		17.4	In the last 12 months of study period: (i) CGI-S scores < 3 for both positive and negative symptoms; (ii) no psychiatric admission; (iii) functional remission.	58.8	CGI-S scores < 3 for both positive and negative symptoms in the last 6 months of the 3-year follow-up
Chang *et al*[91] 2013 Hong Kong	FEP SZ, SZA and schizophreniform disorders	1	104	70.2	73	55.8	44.2	25.8					59.6	RSWG 2005 criteria

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Ciompi[42] 1980 Switzerland	FES	37	1642	18	289	31.8	68.2	75.5			27	Bleuler (1972) criteria		
Ciompi[42] 1980 Switzerland	FES	37	1642	18	289	31.8	68.2	75.5			27	Bleuler (1972) criteria		
Clarke et al [92] 2006 UK	FEP	4	166	79.5	132	58	42	28.5		14.6			57.6	No score higher than 3 over the previous month on any PANSS items at follow up
Craig *et al* [93] 2000 USA	FEP	2	349		335	66.5	33.5	26					47.5	not stated
de Haan *et al*[94] 2008 Netherland	FES spectrum	5	110	94.5	104	84.5	15.5	21.1					37.5	RSWG 2005 criteria
Emsley *et al*[95] 2007 Multicentre	FE SZ, schizophreniform or SZA	2-4	462	46.8	216	72.1	27.9	25.3					50.5	RSWG 2005 criteria
Emsley *et al*[96] 2006 South African	FEP SZ, SZA and schizophreniform disorders	2	57	9.1	28	49	51	28					40	RSWG 2005 criteria

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Evensen *et al* [97] 2012 Norway	FEP	10	301	61.8	184	56.4	43.6	28.1			24.4	A combination of symptom remission and 3 functional dimensions from the SCLFS (independent living, role functioning and social interactions) for 12 months	45.7	RSWG 2005 criteria
Faber et al[98] 2011 Netherland	FEP	2	149	86.6	129	68.5	31.5	25.7			19.4		52.4	RSWG 2005 criteria with an observational period of the last 9 months of a 2-year follow up period and no relapse within 6 months of treatment
Fraguas *et al*[99] 2014 Spain	FES	2			47	72.3	27.7	15.6					53.2	RSWG 2005 criteria
Gasquet *et al*[100] 2008 France	FES	3	933	60.3	563	62.8	37.2	37.5	55.8	27.7			60.6	A score of 3 or less on the CGI-SCH for 6 months or more (i.e. RSWG 2005 criteria)
Gignac et al [101] 2015 Canada	FE Mania	4	101	80.2	81	47.5	52.5	22.3	27.4	6.4	100	A virtual absence of depressive and manic or hypomanic symptoms for 8 weeks	98.8	Criteria for a mood episode were no longer met
Harrison *et al* [102] 2001 Multicentre	FEP	15	1633	61.5	1005	50.6	49.4	47.5			26.1	Bleuler scale & GAF(d) > 60, excluding those with a recent (in the past 2 years) episode of treatment		

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Harrow *et al* [103] 1997 USA	FEP	7.5	276	51.1	141	51	49	23.1					20	Both the absence of major symptoms and adequate psychosocial functioning at any point during the early clinical course
Harrow *et al* [104] 2005 USA	FEP	15	274	57.3	157	50	50	22.8			54.3	Absence of major symptoms, employed (part/full-time) and adequate psychosocial functioning for >1 year, plus no psychiatric re-hospitalisation during the follow up year		
Hassan & Taha[105] 2011 Egypt	FEP	2	56	66.1	37	25	75	17					51.4	RSWG 2005 criteria
Helgason[43] 1990 Iceland	FES	21	107	75.7	81	50.5	49.5	33.5					29	complete psychopathological remission or minor psychopathological symptoms whether in or not in treatment at the end of the study period
Helgason[43] 1990 Iceland	FES	21	107	75.7	81	50.5	49.5	33.5					29	complete psychopathological remission or minor psychopathological symptoms whether in or not in treatment at the end of the study period
Hill *et al*[106] 2012 UK	FEP	12	171	71.9	123	57.9	42.1	29					60.2	RSWG 2005 criteria
Huber *et al*[107] 1980 Germany	FES	22.4	758	66.2	502	42.6	57.4	22.4					22.1	Established according to criteria established by Bleuler (1972)

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Henry *et al*[108] 2010 Australia	FEP	7	723	66.9	484	67.4	32.6	21.9			25.6	The first item was social interactions with people outside of the family (QLS item 4; social activity score ≥4). The second was appropriate role function, defined as paid employment, attending school at least half-time, or, if a homemaker, performing that role adequately (QLS item 9; occupational role functioning score ≥ 4). The third was the ability to perform basic living tasks and to engage in certain activities (QLS item 19; commonplace activities score ≥ 4; eg, shopped for food, paid a bill, gone to a movie or play)	59	The symptomatic severity component but not the 6-moth duration component of RSWG 2005 criteria applied
Jablensky *et al* [109] 1992 Multicultural	FES	1.5-2.5	1379	78.2	1078	54	46	27.9	74				29.4	Complete remission for 76-100% of the time
Johnson *et al*[110] 2014 India	FES	5	113	72.5	95	55	45	29.5					68.4	RSWG 2005 criteria
Jordan *et al*[111] 2014 Canada	FE affective and non-affective psychosis	2	278	57.2	159	67.9	32.1	22.8		8.8			41.5	Scores of ≤ 2 on all 4 SAPS global subscale items (hallucinations, delusions, bizarre behaviour, thought disorder) and SANS global subscale items (affective flattening, alogia, apathy-avolition, asociality-anhedonia).

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Kaleda[112] 2009 Russia	EPET	16.8			278	100	0	17.1					93.9	Psychotic symptoms of insignificant severity (no more than 3 points in the PANSS) with no significant effect on "functioning"
Kinoshita *et al*[113] 2005 Canada	FEP	15	97	53.6	52	55.7	44.3	24.8		18.6	32.7	The state of no symptoms or signs of a psychotic episode for at least 4 weeks		
Kua *et al* [44] 2003 Singapore	FES	20	402	53.7	216	60.7	39.3	23.3	40		28.3	Patient not receiving treatment, well and working (duration not stated)		
Kua *et al* [44] 2003 Singapore	FES	20	402	53.7	216	60.7	39.3	23.3	40		28.3	Patient not receiving treatment, well and working (duration not stated)		
Kurihara *et al* [45] 2011 Indonesia	FES	17	59	72.9	43	58.2	41.8	26.5		60.5			44.2	RSWG 2005 criteria
Lambert *et al*[114] 2005 Germany	FEP	1.5	786	81.8	643	77	33	21.6	49.8				Not stated	No positive symptoms as measured with PANSS for at 8 weeks at the end of follow up
Lambert *et al*[115] 2009 Germany	FEP	3	2960	96.1	2842	49.1	50.9	42.1	43		8.1	Simultaneous fulfilment of the following criteria over a period of at least 24 months: 1) Symptomatic recovery; 2) Functional recovery		

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Lambert *et al*[116] 2006 Germany	FES	2	2960	74.7	2210	49.4	50.6	42.3	42.6				47.2	symptomatic remission defined as receiving a CGI-SZ severity score of absent or mild (score=/<3) for 6b months or longer
Langeveld et al [117] 2012 Norway	FE non-affective psychosis	2	225	83.1	187	62.7	37.3	27.1	44.9				77	A period of at least 1 week without positive psychotic symptoms corresponding to PANSS score of 3 or below on positive symptom items 1,3,5 or 6, or general subscale 9
Lieberman *et al* [118] 1996 USA	FES	5			70	56	44	24.3			84.3		74	No residual symptoms and return to premorbid functioning
Lieberman[119] 1992 USA	FES	5	120	58.3	70	55.7	44.3	24.3		10	84		74	No rating >3 on any of the SADS-C + PD positive psychotic symptoms items, a CGI severity item rating of g3 (mild), a CGI improvement item rating of 2 (much improved) or better, and the maintenance of this level of improvement for 8 weeks.
Lieberman[119] 1992 USA	FES	5	120	58.3	70	55.7	44.3	24.3		10	84		74	No rating >3 on any of the SADS-C + PD positive psychotic symptoms items, a CGI severity item rating of g3 (mild), a CGI improvement item rating of 2 (much improved) or better, and the maintenance of this level of improvement for 8 weeks.
Madsen *et al* [120] 1999 Denmark	FEP	5	63	46	29			28.5					72.4	Patients were considered to be non-remitters if all psychiatric records described a state of permanent psychosis and if that were psychotic at the time of re-investigation

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Manchanda *et al*[121] 2005 Canada	FEP	2	159	57.2	91	71.6	28.4	26.1		74.6	42.1	Rating of 0 on all subscales of SAPS by the end of 1 year in PEPP and maintaining this rating at 2-year follow-up; no period of recurrence of positive symptoms between 1 and 2 years based on consensus rating of independent chart review using a modified version of the Life Chart Schedule	37.5	
Mason *et al* [51] 1996 UK	FES	13	67	86.6	58	62.1	37.9		47		17	Patient is alive, free of psychotic symptoms, no disability, no on treatment in the last 2-years of follow up		
Mattsson et al [122] 2008 Sweden	FEP	5	175	40.6	71	47.9	52.1	29.1			72.2	Living a normal life'' with or without antipsychotic medication and with no need for daily support from professionals. The GAF score had to have been stable at >60 for at least 6 months and they had to have worked or studied independently at least on a half-time basis.		
Morgan *et al*[123] 2014 UK	FEP	10	532	72.7	387	57.9	42.1	30.8	23.6		46	Sustained remission for at least 2 years	77	Absence of overt psychotic symptoms (operationalized as a score of 2 or 3 on Rating Scale 2 in the SCAN; 0=absence, 1=symptom occurred, but fleeting, 2=symptom definitely present, 3=symptom present more or less continuously) for a period of at least 6 months.
Naz *et al*[124] 2007 USA	FE MDD with psychotic feature	4	87		87	41.4	58.6	31.1					69	A period of 8 weeks in which Ps were asymptomatic regardless of treatment status

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Norman *et al* [125] 2014 Canada	FE non-affective psychosis	5	225	70.2	132	77.3	22.7	23.5					88.6	RSWG 2005
Nyman&Jonsson[126] 1983 Sweden	FES	5	110	86.4	95	65.5	34.5	25.9	35		8	"Cured or improved without further relapses"		
Opjordsmoen[127] 1989 Norway	FES	22.5	94			53	47	31.3					16	Not stated
Perkins *et al* [128] 2004 USA	FEP SZ, SZA and schizophreniform disorders	2	191	37.7	72	80.1	19.9	22.4					58.3	Patients who met the following criteria for 4 consecutive weeks were classified as remitters: no rating of >3 (mild) on items P1, P2, P3, P5, and P6 of the PANSS; and a CGI Severity score ≤3 (mildly ill).
Rangaswamy *et al*[129] 2012 India	FEP	2	47	83	39	29.8	70.2	29.7	60	42.6			71.8	PANSS scores were </=60 and GAF score were >80 at the end of follow up; duration not specified
Rangaswamy *et al* [130] 2012 India	FES	25	90	52.2	47	50	50	24.5			14.9	Patients did not have further episodes since the index episode and were functioning well	68.1	At least three consecutive months without psychotic symptoms
Robinson *et al* [131] 2004 USA	FE SZ/SZA	5	118			42	48	25.2			16.4	University of California at Los Angeles recovery criteria. Full recovery required patients fulfilled criteria for both symptomatic remission and adequate social/vocational functioning	54.9	RSWG 2005 criteria without the duration criteria

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Rund *et al* [132] 2015 Norway	FEP	10	301	86.7	261	57	43						79.7	Absence of psychotic symptoms for 1 week
Salem *et al*[133] 2009 United Arab Emirates	FES	6			69	67.6	32.4	27.5			57.4	Not stated		
Salokangas[47] 1983 Finland	FES	8	175	88.6	155	46.9	53.1			70.9	26	Asymptomatic at the end of follow up		
Schimmelmann *et al* [134] 2012 Australia	FEP	1.5	115	86.1	99	48.5	51.5	16.2	57.6				50	Absence of positive symptoms for 12 weeks (Kane et al definition of remission)
Shepherd *et al*[135] 1989 UK	FES	5	121	88.4	107	65	35	34.4	48	76			22	After the key episode became symptom free and remained so throughout the follow up period
Shrivastava *et a*[136]*l* 2010 India	FES	10	200	50.5	101	73.3	26.7	28.8			60	Good compliance (less than 80%), not being hospitalized for a minimum of two preceding years, GAF score greater than 80, QOL score greater than 80, AIMS score less than 2, scores greater than 3 on scales of social functions, independent living, education, and social burden (reverse scored)		

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Simonsen *et al*[137] 2010 USA	FEP	2	301	94.5	293	59.7	40.3	27.8					50.1	Symptoms with score of <4 on any of the PANSS positve subscales items 1, 3, 5, or 6 and on general subscale item 9 for 1 week
Srivastava *et al*[138] 2009 India	FES	10	200	50.5	101						30.5	Assessed with Clinical Global Impression Scale (definition as such not stated)		
Tang *et al* [139] 2014 Hong Kong	FEP	13	153	62.7	96	46	44	31.7	59	25	16.7	Symptomatic remission plus adequate functioning	47	RSWG 2005 criteria duration not stated
Thara *et al* [140] 2004 India	FES	10	90	84	76	50	50	24			14.5	Had not suffered any further psychotic symptoms after the initial admission	48.7	Total absence of all positive symptoms for one months
Thorup *et al*[141] 2014 Denmark	FES spectrum	5	578	52.1	301				39.8		16.9	No psychotic or negative symptoms, GAF(F)>59, in job or education, living independently for the last two years		Minimal–mild positive and negative symptoms on the global scores for SAPS and SANS for at least 6 months

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Tohen *et al*[142] 2012 USA	FE Psychotic Depression	2	56	87.5	49	50	50	36.3		23.2	92.1	A severity rating ≤3 for the DSM-IV A criterion for mania (range 1–7), with no B criterion rated greater than 3 and no two B criteria rated at 3. Patients with initial mixed episodes fulfilled recovery criteria for a manic and a depressive episode (no depression criterion >3, nor more than three at 3). In addition, CGI ratings had to be ≤2; maintained for at least 8 weeks	40.1	Scores < 3 for BPRS-E-Depression subscale items (anhedonia, appetite, care, depression, dysphoria, fatigue, guilt, indecisiveness and poor concentration, motor retardation, suicidal ideation or behaviours) and for BPRS-E-Psychosis subscale items (blunted affect, thought-broadcasting, -control or -withdrawal, conceptual disorganization, disorientation, hallucinations, mannerisms or posturing, suspiciousness, unusual thought content, or emotional withdrawal).
Tohen *et al*[143] 2000 USA	FE Affective disorder with psychotic features	2	219	90.9	199	56.2	43.8	34.1			97.5	A severity rating ≤3 for the DSM-IV A criterion for mania (range=1–7), with no B criterion rated greater than 3 and no two B criteria rated at 3. Patients with initial mixed episodes fulfilled recovery criteria for a manic and a depressive episode (no depression criterion >3, nor more than three at 3). In addition, CGI ratings had to be ≤2; maintained for at least 8 weeks		
Ucok *et al* [144] 2011 Turkey	FES	2	93	47.3	44	52.1	47.9	21.1	43.7				29.5	RSWG 2005 criteria

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Torgalsboen *et al* [145] 2015 Norway	FES	2	28	89.3	25	60.7	39.3	21			16	Symptomatic remission (as adopted from Andreassen *et al*, 2005), plus at least part-time work or school, living independently and at least once weekly socialising with peers or otherwise involved in recreational activities that are age-appropriate and independent of professional supervision all during the last 2 years.	64	RSWG 2005 criteria
van Os *et al* [17] 1996 UK	FEP	1.5	191	87	166	64	36	26.4		12	45	Sustained remission for at least 2 years	60	Absence of overt psychotic symptoms (operationalized as a score of 2 or 3 on Rating Scale 2 in the SCAN; 0 = absence, 1 = symptom occurred, but fleeting, 2 = symptom definitely present, 3 = symptom present more or less continuously) for a period of at least 6 months.
Vazquez-barquero *et al* [146] 1999 Spain	FES	3	86	88.3	76	48.7	51.3		48.7				31.6	Total absence of all psychotic symptoms for at least one month
Verma *et al*[147] 2012 Singapore	FEP	2	1175	66	776	51.3	48.7	28	31.6	22.2	29.4	Patients who fulfilled the criteria for both symptomatic and functional remission	54.1	RSWG 2005 criteria

Author year of publication Country	*Study group*	*FU (years)*	*Sample BL (n)*	*FU Rate (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*Stable relationship BL (%)*	*Recovered FU (%)*	*Definition of recovery*	*Remission FU (%)*	*Definition of remission*
Wade *et al*[148] 2006 Canada	FEP	1			103	71	29	21.6					95.1	A score of 3 or less on all of the BPRS psychotic subscale items for at least 2 weeks
Whitty *et al* [149] 2008 UK	FEP	4	171	75.4	129	65	35	25.5	30				43	no PANSS items >3 for 4 weeks
Wiersma *et al* [150] 2000 Multicentre	FES spectrum	15	496	70.4	349	49	51	42	26	30			40	After one or more episodes no residual symptoms and return to pre-morbid functioning over the first 2 years of follow up
Wiersma *et al* [151] 1998 Netherland	FES	15	82	76.8	63	52	48	25	37				27	Absence of psychotic symptoms, presence of usual pre-morbid functioning for at least 30 days
Wiersma *et al* [151] 1998 Netherland	FES	15	82	76.8	63	52	48	25	37				27	Absence of psychotic symptoms, presence of usual pre-morbid functioning for at least 30 days
Wunderink *et al*[152] 2008 Netherland	FEP	2	125	100	125	68.8	31.2	25.7		15.2	19.2	If both criteria for symptomatic remission (according to RSWG 2005) and GSDS role of functioning score were ≤1, without the symptomatic and functional relapses during the observation period	52	RSWG 2005 criteria for 9 months
Zarate Jr *et al*[153] 2000 USA	FE SZ & schizophreniform	2	30	73.3	22	63.3	36.7	28.9	3.3		86.4	No DSM-III-R 'A' criteria rated >2, and fewer than three criteria rated ≥2 rated on BPRS with duration of 8 weeks or longer		

FU, follow up period; *n*, number; FES, first episode schizophrenia; FEP, first episode psychosis; FEAP, first episode affective psychosis; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAF, Global Assessment of Functioning; GAF(d), Global Assessment of Functioning disability scale; CGI, Clinical Global Impression Scale; CGI-SCH, Clinical Global Impression-Schizophrenia scale; BPRS, Brief Psychiatric Rating Scale; SADS-C, Schedule for Affective Disorders and Schizophrenia a version for measuring the change in symptomology; PANSS, Positive and Negative Syndrome Scale; QLS, Quality of Life Scale; SAPS, Scale for Assessment of Positive Symptoms; SANS, Scale for Assessment of Negative Symptoms; GSDS, Groningen Social Disabilities Schedule; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCLFS, Strauss Carpenter Level of Functioning Scale; SSRG, Scottish Surgical Research Group; UK, United Kingdom; USA, United States of America

The Remission in Schizophrenia Working Group (RSWG) 2005 criteria for remission: Patients were defined as remitters if they demonstrated either a complete absence of psychotic symptoms, or if symptoms were present they were of such low intensity that they no longer significantly interfered with patients' day-to-day functioning. The threshold of symptom severity was as follows: 1) the Positive and Negative Syndrome Scale (PANSS) item scores of ≤3; 2) the Brief Psychiatric Rating Scale (BPRS) item scores of ≤3; or 3) the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms scores of ≤2. As for duration of the remission, a period of 6 months was suggested as a minimum time threshold during which the aforementioned threshold of the symptom severity must be maintained to achieve remission.

There are currently 42 studies that reported on remission rates and 23 reported on recovery rates, with 18 studies reporting on both remission and recovery, for an overall of 83independent samples. The final sample for all of these studies comprised 19,897 FEP patients (range of sample sizes: 20-2,842), with 9,180 (range sample sizes 25-776) with remission data and 10,287 (range of sample sizes 20-2842) with recovery data[2]. I will give an overview of the main findings here.

1.10.4.1. Remission

Remission is an important treatment end point and was previously defined as a complete elimination of the core psychotic symptoms[154, 155]. However, this definition eventually became perceived to be too imprecise without clearly outlined criteria of what constituted "complete elimination of the core psychotic symptoms". Ultimately, it did not recognise the multifactorial nature of SZ, leading to variable or even inaccurate reported rate of remission. In 2005, the Remission in Schizophrenia Working Group (RSWG) derived a consensus definition of remission in SZ [154]. In order to summarise the main criteria for the new definition of remission in a concise and comprehensive manner, I have outlined the detailed proposed criteria for remission as outlined by the RSWG in **Table 2**.

[2] These findings are based on the meta-analyses of remission and recovery rates in FEP, including diagnostic subgrouping, and moderators of remission and recovery that is currently in preparation for submission by John Lally,* Olesya Ajnakina,* Brendon Stubbs, Robin M Murray (in preparation). Remission and recovery from first-episode psychosis in adults: A systematic review and meta-analysis of long term outcome studies.

Table 2 *outlines the newly proposed criteria for remission; specifically the proposed items for Remission criteria with cross-scale correspondence and relationship to historical constructs of psychopathology dimensions and DSM-IV criteria for Schizophrenia. This table is adopted from Andreasen et al [154] and is provided here for illustrative purposes only.*

		Proposed Remission Criteria Items					
		Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS) Items		**Positive and Negative Syndrome Scale Items**		**Brief Psychiatric Rating Scale (BPRS) Items**	
Dimension of Psychopathology	DSM-IV Criterion	Criterion	*Global Rating Item Number	Criterion	*Global Rating Item Number	Criterion	*Global Rating Item Number
Psychoticism (reality distortion)	Delusions	Delusions	20	Delusions	P1	Grandiosity Suspiciousness	8 11
	Hallucinations	Hallucinations	7	Unusual thought content	G9	Unusual thought content	15
Disorganisation	Disorganised speech	Positive formal thought disorder	34	Hallucinatory behaviour	P3	Hallucinatory behaviour	12
	Grossly disorganised or catatonic behaviour	Bizarre behaviour	25	Conceptual disorganisation	P2	Conceptual disorganisation	4
Negative symptoms (psychomotor poverty)	Negative symptoms	Affective flattening	7	Mannerisms/posturing	G5	Mannerisms/posturing	7
		Avolition-apathy	17	Blunted affect	N1	Blunted affect	16
		Anhedonia-asociality	22	Social withdrawal	N4	No clearly related symptoms	
		Alogia	13	Lack of spontaneity	N6	No clearly related symptoms	

* Global Rating Item Number refers to the number used to describe the types of psychotic symptoms in each measure (such as Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS) Items; Positive and Negative Syndrome Scale Items; and Brief Psychiatric Rating Scale (BPRS) Items).

As for duration of the remission, a period of 6 months was suggested as a minimum time period during which the aforementioned threshold of the symptom severity is expected to be maintained for a patient to be classified as a remitter. It was hoped that having clear guidelines for what constituted remission would enable comparison between studies and importantly would help identify why some patients achieve remission while others do not [156]. The rates of remission appear to be very stable despite the different methodologies (i.e., structural face-to-face interviews (on average 55% remitted) or clinical records (on average 57% remitted). The rates of remission did not depend on the use of more stringent criteria such as the RSWG (on average 57% remitted) or the use other criteria for remission (on average 59%).

Nonetheless, despite the consensus criteria of remission as proposed by Andreasen *et al* [154], the rates of reported remission vary considerably from 30% to 80% [74, 157, 158]. Although these differences may reflect the genuine differences in rate of remission, it also may be the case that such a substantial variability may be due to inconsistencies in the criteria for remission applied across studies, such as shortening the period of remission or modifying the threshold of symptoms severity. For example, Larsen *et al* [159] categorised their patients as remitters if they scored ≤4 on specific PANSS items for 2 months demonstrating that 71-76% of their sample were in remission at the end of a 5-year follow up. Wiersma *et al* [50] defined remission as a complete absence of symptoms and return of usual premorbid personality for at least 30 days. Accordingly, only 26.7% of FEP cases were in remission at the end of a 15-year follow up. Malla *et al* [54] defined patients as remitters if they met symptomatic threshold proposed by the RSWG for a duration of one month only, showing that 83% of patents reached remission at the end of a 2-year follow up.

It becomes evident that the operationalised definition of remission has not consistently been applied across a number of studies, making the comparisons of the results very difficult. Recently, in a well-designed longitudinal study, the AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses)-10 study [74], conducted in the UK, the authors defined remission as absence of overt psychotic symptoms (based on SCAN rating criteria) for a period of at least 6 months or longer. Considering that this definition is easier to implement when assessing clinical outcomes and that this study was conducted in the overlapping geographical area as the sample used in my thesis, I will apply the same operationalised criteria for remission. This in turn will facilitate the cross-study comparisons and thus provide a better understanding of the longitudinal course of the illness.

1.10.4.2. Recovery

Recovery is conceptualised as a more demanding phenomenon than remission. Complete recovery implies the ability to function in the community, return of social and vocational functioning and being relatively free of main psychosis symptoms [154]. There are different definitions of recovery available in the literature with consequent variations in the rates of recovery reported among patients with FEP. Some studies focused on absence of psychotic symptoms for a substantial duration as the primary criteria for recovery. For example, in Morgan's *et al* [74] longitudinal study symptom recovery was defined as an absolute absence of any psychotic symptoms for the preceding 2 years or more. It was shown that 46% of FEP patients met criteria for symptomatic recovery during a 10-year follow up. Others utilised Bleuler's (1975) definition for recovery [160]. Accordingly, recovery was characterised with full employment, reassumed social roles and no psychotic symptoms except for some eccentricity or residual symptom. Harrison *et al* [53] showed that 56% of *n*=885 FEP cases met criteria for recovery based on the Bleuler's scale during a 15-year follow up period. In a longitudinal study of 37 years, Ciompi (1980) [42] demonstrated that 27% of all cases met the Bleuler's definition for recovery. More recently, full recovery was operationalised as the absence of major symptoms, plus evidence for adequate psychosocial functioning, including employment (half-time or full-time) and no psychiatric re-hospitalisations. Applying this definition of recovery, Harrow *et al* [161] showed that at the end of a 15-year follow up 41% cases experienced 1 or more periods of recovery. In Robinson's *et al* [162] patients required to fulfil criteria for both symptomatic remission and adequate social/vocational functioning to be considered as recovered. The authors showed that 38.6% met criteria for recovery within a 5-year follow up. Cumulatively, it becomes evident that the rate of reported recovery are varied as are the definition of recovery utilised across studies making it difficult to compare the results and generalise the findings to a winder general patient population.

Table 3. *A review of all longitudinal studies that have examined social outcomes and services use in a sample of patients with first episode psychosis*

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Addington et al[163] 2012 Canada	FES or SZA	2	606	48.5	294	65	35	26.4	54		67.7				
Berg *et al*[85] 1983 Sweden	FES	23.5			20	100	0	26	85	30	90	mean=71 months	20	60	45
Bland & Orn[164] 1978 Canada	FES	14	45	95.6	43	51.2	48.8	32.6		27.9	79	mean=744 days; median=4 23 days		30	
Bottlender *et al* 2010 UK	SZ	15	61			41	59	32.2						20	79
Ceskova *et al* [165] 2011 Czeck Republic	FES	7	76	57.9	44	100	0	22.2							
Ciompi[42] 1980 Switzerland	FES	37	1642	18	289	31.8	68.2	>65.0					38	43	49
Craig *et al* [93] 2000 USA	FE SZ & SZA	2	155	96.1	149	66.5	33.5	26		20.6	53.5				
Cullberg *et al* [166] 2006 Sweden	FES	3	71	85.9	61	62	38	27.7		17		mean=34 nights		50	
DeLisi *et al* [167] 1992 USA	FES	2	50	58	29	64	36	26.2				mean=4.2 months			

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Geddes *et al*[168] 1994 UK	FES	7	51	84.3	43	51.2	48.8	27.3			81				
Gignac *et al*[101] 2015 Canada	FEM	4	101	38.6	39	47.5	52.5	22.3	27.4	6.4				33.3	5.1
Harrison *et al* [102] 2001 UK	SZ	15		88.7	502	50.6	49.4	41.4					37		
Harrow *et al*[103] 1997 USA	FES	7.4	74		71	36	64	23.1			29			20	
Helgason[43] 1990 Iceland	FES	21	107	75.7	81	50.5	49.5	33.5			80	mean=106 days	17.3	46.5	
Henisz[169] 1966 Poland	FES	7	249	84.7	211	43.4	56.6	31.6			71.5				
Henry *et al*[108] 2010 Australia	FEP	7	723	66.9	484	67.4	32.6	21.9						39.2	18
Hill *et al* [106] 2012 UK	FEP	12	171	71.9	123	57.9	42.1	29						37.7	
Ho *et al*[170] 1998 USA	FES	2	50	100	50	64	36	23.9						60	

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Jab *et al* [171] 2004 Germany	FES	13			77	43	57	38.4				48.2 weeks	26.5	45.5	32.6
Jablensky et al[109] 1992 Multicultural	FES	18-30 months	1379	78.2	1078	54	46	27.9	74		69				
Johnstone *et al*[172] 1990 UK	FES	2	253	93.7	237									49.4	
Kaleda[112] 2009 Russia	EPET	10			278	100	0	17.1						62.9	25.2
Kam *et al* [173] 2015 UK	FEP	3.6	182	88.5	161	74	26	22.4						27	
Kua *et al* [44] 2003 Singapore	FES	20	402	53.7	216	60.7	39.3	23.3	40					32.4	
Lambert *et al* [116] 2006 Germany	FES	2	2960	74.7		49.4	50.6	42.3	42.6						
Manchanda *et al* [121] 2005 Canada	FEP	2	not known	not known	24	91.7	8.3	23.3		95.8	64				

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Mason *et al* [51] 1996 UK	FES	13	67	86.6	58	62.1	37.9		47		28.9		28	37	
McCreadie *et al* [174] 1989 UK	FES	2	49	77.6	38				79		47			42	
Moller *et al*[175] 2002 Germany	FES	15	184	41.3	76	36.8	63.2					mean=8.3 months			
Morgan *et al* [123] 2014 UK	FEP	10	532	72.7	387	57.9	42.1	30.8	23.6		70.4	median=48 days		22	31.7
Munk-Jorgensen and Mortensen[176] 1992 Denmark	FES	15	53	67.9	36	43.4	56.6	28.5	21.4				69.4	16.7	
Nyman&Jonsson[126] 1983 Sweden	FES	7.5	110	86.4	95	65.5	34.5	25.9	35				33.9	56.6	29.5
Opjordsmoen[127] 1989 Norway	FES	22.5			94	53	47	31.3						20	43
Racenstein *et al*[177] 2002 USA	FES	10	70			64	36							13	

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Rangaswamy *et al*[129] 2012 India	FES	25	90	52.2	47	50	50	24.5						63.8	63.8
Rupp and Fletcher 1940 USA	FES	4.5-10	641	81	608	53	47				85.4				
Salem *et al*[133] 2009 United Arab Emirates	FES	6	69			67.6	32.4	27.5			78.3				
Salokangas[178] 1996 Finland	FES	5	227	79.3	180	48.9	51.1			26.3			52.3		33
Salokangas[47] 1983 Finland	FES	8	175	88.6	155	46.9	53.1			70.9		mean=283 .8 days		31.8	39
Sarotar et al[179] 2008 Slovenia	FES		87			47.1	52.9	39.5							
Schimmelmann *et al*[134] 2012 Switzerland	FEP	1.5	99	100	99	48.5	51.5	17.1	57.6					46.7	
Shepherd et al[135] 1989 UK	FES	5	121	88.4	107	65	35	34.4	48	76	55	mean=53. 3 weeks		48	84
Shrivastava *et al* [180] 2011 India	FES	10	200	55	101	73.3	26.7	28.2	25.7					25	

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Sim et al[181] 2007 Singapore	FES	2	254			55.1	44.9	28.8	12.2	14.2		mean=27 days			
Singh *et al* [182] 2000 UK	FEP	3	166	86.1	143	59	41	30.8	25.3		80.1	mean=81.58 days			
Soskis *et al*[183] 1968 USA	FES	5	39	82.1	32	41	59	25.4			50		16	90.6	
Srivastava *et al*[138] 2009 India	FES: Improved recovery at 10 years	10			61	70.5	29.5							40	
SSRG 1992 UK	FES	5	49	85.7	42				65			mean=8.2 months		19	88
Stirling *et al* [184] 2003 UK	FEP	10	112	62.5	70	56.3	43.7	26.3						22.4	
Takei *et al*[185] 1998 UK	FEP: Black ethnicity	18	34		32		71.9	28.1				mean=255 days			
Takei *et al*[185] 1998 UK	FEP: White ethnicity	18	54		49		57.1	42.9				mean=89 days			
Tang *et al*[139] 2014 Hong Kong	FEP	13	153	62.7	96	46	44	31.7	59	25			9	32	32

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Thara *et al* [140] 2004 India	FES	10	90	84	76	52.6	47.4	24					2.6	10	
Tohen *et al*[143] 2000 USA	FE Major Affective disorder with psychotic features	2	229	90.9	199	56.2	43.8	34.1						50.7	25.1
Turner *et al*[186] 2009 New Zealand	FEP	2	236			72.5	27.5	22.4	40.5	8				63.6	
Ucok *et al*[144] 2011 Turkey	FES	4	94	46.8	44	52.1	47.9	21.1	43.7			mean=47.8 days			
White *et al* [48] 2009 UK	FEP	10	109	63.3	69	59	41	27.4	19	18	82			16	
Whitty *et al* [149] 2008 UK	FEP	4	171	75.4	129	65	35	25.5	30			mean=92.8 days		36	6
Wiersma *et al* [151] 1998 Netherland	FEP	15	82	76.8	63	52	48	25	37		56				
Wiersma *et al*[150] 2000 Netherland	FES spectrum	15	496	70.4	349	49	51	42	26	30			25	20.4	22.4

Author year of publication Country	*Study groups*	*length of FU (years)*	*Sample BL (N)*	*Rate of FU (%)*	*N FU*	*Male (%)*	*Female (%)*	*Mean age*	*Employed BL (%)*	*In relationship BL (%)*	*Re-hospitalised FU (%)*	*Length of inpatient stays*	*Living alone FU (%)*	*Employed FU (%)*	*In relationship FU (%)*
Wieselgren & Lindstrom[187] 1996 Sweden	FES	5	120	84.2	101	72	28	27.1	37		85	total 16.5 months		26	
Zhang-Wong *et al* [188] 1995 Canada	FEP	5	176	71	123	45.5	54.5	23.3					56.6	40.2	

FU, follow up period; BL, baseline; *n*, number; FES, first episode schizophrenia; FEP, first episode psychosis; SZ, schizophrenia; SZA, schizoaffective disorder; RSWG, Remission in Schizophrenia Working Group; DSM, Diagnostic and Statistical Manual of Mental Disorders

1.10.4.3. Service utilisation

In the AESOP-10 study [74] it was highlighted that 12% of *n*=388 FEP patients were never admitted to hospital at any point, 18% were admitted at initial presentation only and 70% were admitted at least once during the 10 year follow-up. The authors further showed that the median length of admission was 48 days, and the proportion of the follow-up spent in hospital was around 14 weeks over an average of 520 weeks (10 years) of follow-up. Helgason [43] in a 20-year follow up of *n*=107 first time admitted SZ patients showed that 80% of the sample was admitted at least once during the follow up period. Similar findings were reported by Harrison *et al* [53] in a 15-year follow up of *n*=1,171 FEP cases. White *et al* [48] reported that 18% of *n*=109 FEP patients had no further admissions after first contact with mental health services but a minority had more than 10. Cumulatively, these findings show that the treatment for psychosis places a substantial burden on services with consumption of resources for many years after first onset of illness.

1.10.4.4. Social outcomes

Social outcomes encompass functioning in everyday situations, capacity for independent living and social interactions [189], maintaining employment and stable relationships during a follow up period. Kua *et al* [44] showed that of *n*=277 FEP cases 53.2% were unemployed at the end of a 20-year follow up period. In a similar 20-year follow up study, Helgason [43] demonstrated that only 17% of SZ cases were employed full-time, 41% did not have close friends and 51% remained single or unmarried. In White *et al*'s [48] study it was shown that 48% of all patients never worked during a 10-year follow up. In Mason *et al*'s [51, 52] research spanning over 13 years, 28% of all patients lived alone and 44% lived on disability benefit for a mental condition at the end of follow up period. Ciompi [42] showed that at the end of a 37-year follow up 83% were either single, separated or divorced. In Crumlish's *et al* [56] study, 65.7% were living with parents or other family and 9% lived in either hostels, supported accommodation or were homeless. In the more recent AESOP-10 study, Morgan *et al* [74] demonstrated that only 12% of patients were employed for 75% of follow up time; in terms of relationships, 71% remained single during the follow up period and 68% were single at the end of a 10-year follow up period. Cumulatively, these studies provide compelling evidence that psychosis is often associated with deterioration in social and occupational functioning in the decades after first onset.

1.11. Treatment resistance (TR) as an important outcome

Response to treatment or lack of thereof is one of the most important clinical outcomes of psychosis that needs to be considered. Although 'response to treatment' has no universally accepted research definition, it is recognised clinically as a substantial reduction of symptoms, usually accompanied by functional improvement following a treatment with antipsychotic medications. Around 30% of patients diagnosed with SZ [190] [191] fail to respond to two antipsychotics after adequate trials. These patients are defined as having treatment resistance (TR). Clozapine is the only evidence-based effective medication for TR. In the UK, it is recommended that clozapine be offered to people with SZ whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic medications[192].

1.12. Limitations and gaps in available follow up studies of outcomes in FEP

There are a few important gaps in current research on longitudinal outcomes in patients with first episode psychosis. I will review the main gaps here.

1.12.1. Methodological heterogeneity

Current studies that set out to explore longitudinal outcomes in patients with FEP are marked by methodological heterogeneity making the comparisons of the results and drawing inferences of the nature and progression of psychosis over time challenging.

1.12.2. Studies of longitudinal outcomes and Ethnicity are sparse

The potential reasons for the higher rate of incidence of psychosis observed among Black African and Black Caribbean populations residing in the UK than in their White counterparts[59-61] are still the subject of debate and controversy, especially when it was shown that it was not an artefact of misdiagnosis [193] nor differences in genetic predisposition to this disorder [66, 69]. Although the precise mechanisms of this disparity are not known, this heterogeneity is further reflected in the the patterns of treatment delivered to the patients from different ethnic backgrounds. There is evidence to suggest that on first contact with

mental health services patients of Black ethnicity are more likely to be admitted to a hospital under the Mental Health Act (MHA) 1983 [62], have police present either during or shortly before an admission to a psychiatric unit [69, 194], or to be admitted to high-security psychiatric hospitals [195] compared to patients of White ethnicity.

The evidence is also accumulating that this pattern of care in Black ethnic group persists over time. It has been shown that patients of Black Caribbean and Black African ethnicity have higher rates of detentions under the MHA over a 2-year follow up period [196]. Patients of Black ethnicity were more likely to have been re-admitted at least once [197], and to have experienced longer hospitalisations over a 18-year follow up compared to patients of White ethnicity. Cumulatively, these results may portray an illness trajectory characterised by a more degenerating course in patients of Black ethnicity compared to patients of White ethnicity. However, the current research into the clinical illness course across different ethnic groups is sparse to allow us to make any inferences about the clinical course and outcomes in different ethnic groups in the UK. While it is well-established that one-third of the patients with severe psychotic disorders recover, it is not known what proportion of these constitutes Black ethnic minorities. Reports are also mixed in relation to remission in Black populations with some reporting that remission is more common in Black ethnic groups [198], while others argue an opposite view [199]. In general, research into the ethnic differences in longitudinal clinical outcomes in different ethnic groups in the UK is marked with the methodological differences. Many studies were limited by small sample sizes [196], and there was a tendency to neglect the diversity in culture, religious beliefs and life experience between Black African and Black Caribbean populations by combining these ethnic groups in analyses [185, 196-198]. Some limited their sample to those with diagnosis of schizophrenia [69, 197]; such designs bias samples towards those with poorer outcomes [49]. Ultimately, previous research has not provided us with a comprehensive picture of the true course of psychotic disorders after the first onset across ethnic groups resident in the UK.

1.12.3. Length of follow up

Among the identified studies that I presented in Table 1 and 3, the duration of follow up varied from study to study. Some studies focused on 1-2 years [35, 54, 200], others on 3-5 years [55, 76, 159, 162, 201-203], 10-15 years [46, 48, 50-53, 57, 161, 177, 204, 205], others up to 20 years [44, 45, 185] or 40 years [42]. Ultra-long-term studies are more likely to be limited by high levels of drop-outs that may occur not completely at random [49] leading to attrition bias. Indeed, some have argued

that the first 3-5 years after first onset of illness constitute a critical period in determining long-term outcomes [202] [56] beyond of which the level of sustained disability endures into the long term [206]. Therefore, in this thesis I will focus on the first 4-5 years of the illness after first contact with metal health services for psychosis.

1.12.4. Dearth in understanding the risks for TR

At present it is not possible to predict those who will or will not respond to first line of antipsychotic treatments. Early identification of patients who require clozapine has the potential to improve clinical outcomes and minimise the social and functional disability that results from prolonged psychotic illness [207-209]. Although a few potential risk factors for TR, such as poor premorbid functioning, longer DUP, increased negative symptoms and a younger age of illness onset, have been suggested [191, 210-212], the predictive value of specific clinical and demographic factors on TR has not yet been widely investigated [213]. While there is a large literature investigating predictors of treatment response and remission from illness onset [191], TR has not been examined longitudinally as an outcome measure in FEP. Additionally, there is a considerable dearth of information on whether those patients who subsequently developed TR were resistant from the start of the illness or gradually progressed to it. Knowing the exact rates of early resistance or late resistance of those with TR may be an important finding with important implications in relation to the delay in clozapine use which exists in clinical practice [214], and aetiology of such complex phenomenon as treatment resistance.

1.12.5. Prediction of time to remission

Remission is one of the best indicators of treatment efficacy and response [156]. However, predicting who will remit still remains challenging. In examining the potential predictors of remission, earlier studies tended to focus either on rates or odds of remission occurring [215, 216], and as such they are limited in their ability to tell us how long it would take for the patients to achieve clinically-viable remission after first contact with mental health services. Knowing which groups of patients will take longer to regain their pre-morbid functioning could direct clinicians to seek more effective treatment strategies from the start. Previously, it has been shown that time to remission was influenced by age of illness onset and duration of untreated psychosis [217]. However, the influence of symptom dimensions expressed at baseline on time to first remission has not yet been investigated. Although it has been

argued that combining the traditional operationalised diagnostic categories with the psychosis dimensions will lead to a number of benefits no studies to-date have tested whether combining symptom dimensions with categorical diagnoses led to a more robust model for predicating time to first remission.

1.13. Conclusion

The wide variability in treatment response, clinical and social outcomes in patients with FEP can be understood by viewing psychotic disorders as a heterogeneous collection of illnesses with diverse clinical presentations and response to pharmacotherapeutic interventions. However, our current understanding of the outcomes in FEP is limited, especially when it comes to patients of Black ethnicity, which may at least partially be related to methodological heterogeneity, lack of consistency in inclusion criteria or length of follow-up, definitions of outcome and a paucity of epidemiologically robust studies of FEP cohorts. Therefore, detailed and hypotheses-driven research is required to establish the basis for improving our understating of the longitudinal trajectory of psychotic disorders.

AIMS AND HYPOTHESES

1.14. The aims of the thesis are:

1.1. To identify the proportion of patients with FEP who had first presented to the 'at risk' services with the ARMS and who, by definition, subsequently transitioned to first episode psychosis.

1.2. To investigate whether there were significant differences in pathways to care, clinical presentations and social circumstances between FEP patients with and without prior contact with the ARMS services at the time of first contact with mental health services for psychosis.

1.3. To investigate whether pathways to care, clinical presentations and social circumstances significantly differed between two groups of patients with FEP, those who did not have prior contact with the ARMS services and those patients who were already experiencing a full psychotic episode at the time of first contact with the prodromal services.

2.1. To identify to what extent the psychosis symptom dimensions in FEP patients influence the time to first remission after first contact with mental health services with psychosis.

2.2. To investigate whether combining symptom dimensions with categorical diagnoses rather than using these predictors separately would lead to a more robust model for predicating time to first remission during the first four years after first contact with mental health services for FEP.

3. To establish whether the clinical outcomes and service utilisation differed in Black African and Black Caribbean ethnic groups compared to White British patients during first five years after first contact with mental health services.

4.1. To identify baseline clinical risk factors predictive of treatment resistance (TR) during the first five years of illness in first-episode schizophrenia spectrum patients.

4.2. To identify a proportion of TR patients who showed “early-resistance” (E-TR) and those with “late-resistance” (L-TR).

4.3. To investigate the differences in socio-demographic and clinical presentations between patients subgroups with E-TR and without treatment resistance (non-TR), and those with L-TR and those who were non-TR.

4.4. To compare sociodemographic and clinical characteristics at the time of first contact with mental health services between the TR patients treated with clozapine and those FEP patients who met the criteria for the TR but had not received clozapine.

1.15. The hypotheses of the thesis are:

1.1. The prodromal services in South-East London established close links with primary care providers and non-health related community services, such as schools, counsellors, and emergency and criminal justice agencies, thus creating an accessible and acceptable service for help-seeking young people who are at risk of psychosis [28, 38], I therefore hypothesise that the proportion of FEP patients who had prior contact with the prodromal services before subsequently transitioning to first episode psychosis will be high.

1.2. Because the prodromal services in South-East London are dedicated to reducing the length of DUP by detecting the ‘high-risk’ of transition individuals[28, 34, 35] I hypothesise that at the time of first contact with early intervention services for first episode psychosis, DUP will be significantly shorter in those patients who had first presented to the ‘at risk’ services with the ARMS and who subsequently transitioned to first episode psychosis compared to the FEP patients who did not have a prior contact with the ARMS team.

1.3. Because of the close links between the prodromal services in South-East London and primary care providers I hypothesise that a greater proportion of patients with FEP

who had first presented with the prodromal services with the ARMS before making the transition to first episode psychosis will be referred to the standard services for FEP by health professionals rather than via emergency and forensic teams

2.1. There is a growing consensus that psychosis symptom dimensions may be more useful in providing information about need for care and prognosis[218-220]; therefore, I hypothesise that psychosis symptom dimensions in patients with FEP as measured at the time of study entry will predict speed of remission during the early course of illness

2.2. Similarly to 2.1., because psychosis symptom dimensions may be more accurate in providing information about need for care and prognosis compared to the traditional diagnostic categories [218-220]; I hypothesise that psychosis symptom dimensions measured at baseline will provide a more accurate prediction of time to first remission than traditional diagnostic categories during the follow up period.

2.3. As it has been shown that combining dimensional measures with categorical diagnoses is more informative than considering them separately [218] my hypothesis is that combining dimensional with traditional diagnostic approaches in predicting time to first remission will provide more robust and sensitive predictors of time to first remission than using these predictors separately during the follow up period than either used separately.

3. There is some evidence in the literature that individuals of Black ethnicity are more likely to make contact with mental health services via admissions under Mental Health Act (MHA) legislation[62] , in many cases with police present on an admission [69, 194], or admission to high-security psychiatric hospitals [195] , compared to White British patients. However, attempts have been in recent years to address these issues. Therefore, I hypothesise that the clinical course and pattern of care in patients of Black ethnicity would not be different from patients of White British ethnicity during the first five years after first contact with mental health services for psychosis.

4. In the current literature, a few potential risk factors such as poor premorbid functioning, longer DUP, greater severity of negative symptoms, and a younger age of illness onset, have been suggested as important contributing factors for onset of for treatment resistance [191, 210-212]. Therefore, my hypothesis is that baseline clinical and

social risk factors including type and severity of symptoms, gender, age at illness onset, ethnicity, DUP will be important predictors of treatment resistance defined at the end of the first five years of illness in first-episode schizophrenia spectrum patients.

CHAPTER 2 METHODOLOGY

2.1. Introduction

The data presented in this thesis is drawn from two independent studies of first episode psychosis: 1) EUropean network of national schizophrenia networks studying Gene-Environment Interaction (EU-GEI) study which was initiated as part of the National Institute of Health Research (NIHR); and 2) Genetics and Psychosis (GAP) study which was, similarly to the EU-GEI study, part of the NIHR Biomedical Research Centre (BRC) conducted in South London, UK. In this chapter I will provide a detailed description of each of these two studies beginning with the data collection and assessments and finishing with an outline of my personal contributions to both studies. In the first part of this chapter (section 2.2) I focus on the EU-GEI study. I have utilised the data collected as part of the EU-GEI study in the Study 1 (Chapter 3, page 81-92). All subsections related to 2.3 section are dedicated to the GAP study.

2.2. Overview of the EU-GEI study

2.2.1. Study design. I compared sociodemographic clinical characteristics including DUP and pathways to care in patients attending the Outreach and Support in South London Service (OASIS), a specialised community mental health service for people with the ARMS for psychosis [28, 37] (i.e., PROD group) with FEP patients without a prior contact with the OASIS service before their first contact with mental health services for FEP (i.e., FEP-C group). I additionally derived a third group which included patients who were found to be already experiencing their FEP at the time of first contact with the OASIS (i.e., FEP-P group).

2.2.2. Sample. The total sample comprised of *n*=338 patients with FEP. Participants aged up 18 to 65 were recruited as part of the NIHR EU-GEI study and who presented to mental health services in the South London and Maudsley National Health Service (NHS) Foundation Mental Health Trust between 1 May 2010 to 1 May 2012 with a FEP (International Classification of Diseases [ICD-10] codes F20-F29 and F30-F33) (World Health Organisation [WHO], 1992). However, in my analyses I only included patients aged up to 35 years plus 2 years allowing them to develop FEP as only they had had the opportunity to attend the ARMS centre. The patients were included in the study if they were

current residents of Lambeth (population 303,086) or Southwark (population 288,238) boroughs served by the Trust. Exclusion criteria were: 1) evidence of psychotic symptoms precipitated by an organic cause; 2) transient psychotic symptoms resulting from acute intoxication as defined by ICD-10; 3) head injury causing clinically significant loss of consciousness; and 4) learning disability (IQ<70).

2.2.3. Data sources. The patients were identified from electronic records obtained from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register Interactive Search (CRIS) system [221] [222]. Using specific search terms, the CRIS system allows researchers to search the SLaM Patient Journey System which is a comprehensive record of all clinical information recorded throughout patients' journeys through the Trust services. It includes information on demographic characteristics and clinical presentation on first contact and onwards, dates and other details of referrals, detailed clinical assessments, care plans and medication, clinical activity and reviews[221, 222]. The CRIS application was developed in 2007–2008 and consists of a series of data-processing pipelines which both structure and condense effectively anonymised data from the full available clinical records [222]. Using the CRIS system, I and members of the team who worked on identification of first episode psychosis patients as part of the EUGEI study under supervision of Prof Craig Morgan identified all patients who came in contact with SLaM for FEP over 2 year period (i.e., 2010-2012). We applied search terms such as “hallucinations”, “psychotic”, “delusions”, “voices”, “delusions”, etc. We read through the notes for all records that these search terms extracted on one-to-one basis in order to ensure that all patients included in the study met the inclusion criteria for FEP. Where there was ambiguity about the FEP status of a patient, a consensus decision was made; this always included those with long-standing expertise in the study of first episode psychosis (C.M.).

Once a cohort of FEP patients has been identified, I then proceeded to extract information on their socio-demographic characteristics, clinical presentation and pathways to care on the first presentation to mental health services from electronic records using the BRC CRIS system [221]. I further utilised the BRC-CRIS to identify those patients from my cohort of FEP cases who were referred to the Outreach and Support in South London Service (OASIS), a specialised community mental health service for people aged 14-35 years old with the ARMS for psychosis [28, 37] services and who, having met criteria for the ARMS, were accepted for treatment prior to making the transition to FEP. CRIS was approved as a data resource for secondary analysis by the Oxfordshire Research Ethics Committee (reference 08/H0606/71).

2.2.4. Assessments

An exact copy of the measure that I used to collect information on all the variables listed in this section is presented in Appendices (page 187).

2.2.4.1. Socio-demographic characteristics. The Medical Research Council (MRC) Socio-demographic Schedule (modified version) was utilised to collect data on socio-demographic characteristics and cannabis use [223].

2.2.4.2. Ethnicity. Ethnicity was self-ascribed as was recorded in the clinical notes by the treating clinicians and was further classified using the 16 categories employed by the 2011 UK Census (http://www.ons.gov.uk/ons/guide-method/census/census-2011/index.html). In the present study I combined these into three broad ethnic groups: White (all white groups), Black (all black groups), and Other (encompassing Asian, mixed and other ethnicities).

2.2.4.3. Duration of untreated psychosis (DUP) was defined as the difference between the date of an appearance of first symptoms of psychosis, such as positive symptoms and date of a start of first treatment with antipsychotic medications [224]. *Age at first contact* was defined as the age at which a patient was in contact with mental health services for the first time due to their psychotic symptoms [198].

2.2.4.4. Mode of onset. Similarly to previous studies [225, 226], mode of onset of psychotic symptoms was operationalised using definitions developed in the World Health Organisation International Pilot Study of Schizophrenia, and was categorised into three main groups: 1) *acute* (psychotic symptoms appeared within hours, 1 week or 1 month of first noticeable behavioural change); 2) *gradual* (psychotic symptoms appeared within period of 1 to 6 months of first noticeable behavioural change); and 3) *insidious* (psychotic symptoms appeared incrementally over a period of 6 months or greater since first noticeable behavioural change).

2.2.4.5. Pathways to Care. In the present study, four most commonly used pathways were examined: 1) general practitioner (GP); 2) emergency medical services (primarily accident and emergency departments, walk-in centres); 3) criminal justice agencies (police, prison or

probation services and courts); and 4) health workers (social support workers, nurses or other mental health workers).

2.2.5. Analyses

The distributions of socio-demographic characteristics, clinical presentation and pathways to care were explored with frequencies, percentages, mean and standard deviation, median, range and IQR. The comparisons between the groups were made using x^2 test and ***Fisher's*** exact test for categorical data and *t*-test for continuous data. DUP was heavily skewed and was consequently log-transformed to allow parametric analyses. DUP for each group of patients is presented in the original scale, while the analyses were conducted using the logarithmic-transformed values.

2.3. Overview of the GAP study

The research participants used were recruited as part of the GAP study the aim of which was to explore the genetic and environmental basis of liability to psychosis. Patients with first episode of psychosis (FEP) and healthy participants were recruited from the boroughs covered by the SLaM NHS Foundation Mental Health Trust which encompassed: Croydon (population 342,800), Lambeth (population 303,086), and Southwark (population 288,238) (UK government national statistic; http://data.london.gov.uk/datastorefiles/visualisations/atlas/fol10-pop&mig-2010/atlas.html).

2.3.1. Ethical approval and consent procedure

The GAP study was granted ethical approval by the South London and Maudsley and Institute of Psychiatry Local Research Ethics Committee (Ethics reference number: 05/Q0706/158). All participants were presented with a study description and consent form which contained the following information: 1) consent for the acquisition of whole blood for extraction of DNA, RNA, serum and development of cell lines for molecular and biochemical studies; 2) for accessing the clinical records; and 3) consent for further contact. It was emphasised that there would be no penalties if the participants decided to withdraw from the study at any point. If the participants were happy to participate, they were asked to sign the informed consent.

2.3.2. Study design at baseline

Initially, the GAP study had a case-control (or cross-sectional) study design where potential participants were selected on the basis of whether they had or did not have the outcome of interest (in this instance, first episode psychosis). This in turn allowed hypotheses concerning potential risk factors for the illness to be investigated by comparing the prevalence of "exposures" in those with and those without the "outcome" of interest. The primary benefit of employing this study design was that it is less expensive and more time efficient to employ a large pool of such patients compared to the prospective study designs, as it was not necessary to wait for the development of the disorder (outcome). Importantly, a case-control study only requires large sample sizes when the prevalence of the exposure to the risk factor in the controls is very rare (<20%) or very common (>80%)[227]. Though, a few important limitations that are inherent to this study design are noteworthy such as selection bias.

2.3.3. Recruitment of FEP cases

A team of trained researchers weekly screened all inpatients units and outpatient mental health services within the catchment areas to identify the eligible cases. All patients aged 18-65 years and who presented to inpatient and outpatient psychiatric services of the Trust between December 2005 and October 2010 with FEP, as per International Classification of Diseases (ICD)-10 (F20-F29 and F30-F33) [228] criteria and further validated by administration of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), were approached by researchers and were invited to take part in the GAP study. Potential cases were excluded if they exhibited evidence of 1) psychotic symptoms were most likely to have arisen from an organic cause; 2) transient psychotic symptoms which resulted from an acute intoxication as defined by ICD-10; 3) head injury experienced at any time in their life prior to recruitment to the GAP study causing clinically significant loss of consciousness; and 4) learning disability (IQ<70).

Within the study period, 606 patients with FEP were approached. Of these 606 patients, 145 (24%) refused to participate resulting in total of *n*=461 patients with FEP cases recruited. The two most common reasons for refusal were lack of interest in the research and the length of the baseline assessments [229]. Patients who refused to participate were more likely to be men (*p*=0.04) and of Black Caribbean and Black African ethnic origin (*p*=0·001) than

were those who consented [229]. If patients with FEP were too unwell to cooperate at the time of recruitment, they were re-contacted once following initiation of treatment. The full information on socio-demographic characteristics at baseline was available for 449 (97.4% of 461) consented cases.

2.3.4. Assessments at baseline

2.3.4.1. Socio-demographic characteristics. The Medical Research Council (MRC) Socio-demographic Schedule modified version[223] was utilised to collect data on socio-demographic characteristics (age, gender, level of education attainment, employment status, etc.) for FEP cases and healthy controls.

2.3.4.2. Age at first contact was defined as age at which a patient was in contact with mental health services due to onset of first psychotic symptoms [198].

2.3.4.3. Ethnicity. Ethnicity was self-ascribed from the 16 categories employed by the UK Census in 2001 (www.statistics.gov.uk/census 2001). For the purposes of the present thesis I further subcategorised the sample to four broad ethnic groups [230]: 1) White British ethnic group which included the subcategories of: White English, White Welsh, White Scottish and White Northern Irish; 2) White Other ethnic category included all patients of White ethnicity that were not of White British ethnicity; 3) Black African category included all Black participants born in sub-Saharan Africa or born in the UK with at least one parent of sub-Saharan African origin; and 4) Black Caribbean category comprised all Black individuals born in the Caribbean or born in the UK with at least one parent of Caribbean origin; and 5) "Other" ethnic group encompassed Asian, mixed-ethnicity and other ethnicities.

2.3.4.4. History of substance use. Information was collected on history of alcohol use administering the Alcohol Use Disorders Identification Test (AUDIT) [231]. From February 2006 onwards the collection of a detailed history of cannabis use was implemented by adding to the study assessment the Cannabis Experience Questionnaire modified version, $CEQ_{mv,}$ [232]. The CEQ_{mv} included several questions covering the use of stimulants or any other non-prescribed drugs. For those patients with FEP who were inpatients at the time of recruitment a period of 4 weeks prior to the hospital admission was considered as the abstinence period.

2.3.4.5. Baseline diagnosis. Diagnoses at baseline were made utilising the Operational Criteria Checklists (OPCRIT) [233]. The OPCRIT system consists of a 90-item checklist and uses computerised diagnostic algorithms based on published criteria to provide a diagnostic category for each subject employing a number of classification systems [233].

2.3.4.6. Psychotic symptoms. The Positive and Negative Syndrome Scale (PANSS [234]) was completed in face-to-face interviews with the patients to assess psychotic symptoms over the week preceding the assessment. The 30 items are each rated on a 7-point scale (1=absent, 7=extreme) and grouped into three subscales: positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items). A higher score indicates more severe psychopathology over the last 7 days prior to the interview. The inter-rater validity for this measure between the researchers was higher as highlighted above than the conventionally accepted thresholds for the adequate inter-rater agreement (r=0.814).

2.3.4.7. Duration of untreated psychosis (DUP). DUP was determined from the assessment interview and mental health records and defined as the difference between the date of the appearance of the first positive psychotic symptom (hallucination, delusion or thought disorder rated as 4 or higher on the PANSS [234] as per Singh *et al.*[235] and date of initiation of first treatment with anti-psychotic medications [226]. The standard rule of thumb was employed when trying to attain information on dates in the most reliable manner [235]; specifically, using the actual dates when known, or using the middle of the months (i.e., 15th) when only the month was known or the middle of the year (i.e., 1st of July) when a given year was known only.

2.3.4.8. Global Assessment of Functioning (GAF). GAF was used to measure both overall symptoms severity and disability associated with the illness severity at study entry [236]. The GAF measure is a widely used observer-rated instrument to rate clinical and functional status on a scale ranging from 1 to 100. The scale is hypothetical indicating either hypothetically the sickest individuals (≥1) or the healthiest (≤100). Even though, the scale is further subdivided into 10 equal parts and provides defining characteristics for each 10-point interval, a rater is required to assign the exact number on the continuum. The GAF was rated following face to face interview for patients with psychosis to ascertain the severity of their psychotic symptoms and level of social functioning over the last 7 days before the baseline interview.

2.3.5. Tracing collection at follow up

Approximately 4-5 years after first contact with mental health services for psychosis, I sought to trace all cases who had given their consent for follow up and for their clinical records to be accessed for research purposes. The following methods were used in the process of tracing the patients:

2.3.5.1. Electronic psychiatric clinical records (EPCRs)

For those patients who were still in contact with the local mental health services, or who were discharged following completion of a treatment program, the primary source of information on outcomes over the course of the follow up period was the electronic psychiatric clinical records (EPCRs). The EPCRs are the primary clinical recordkeeping system in the South London and Maudsley NHS Foundation Trust. The EPCRs contain a detailed mental state assessment, success of the treatments and a structured summary of care delivered. Progress notes recorded the on-going care with the dates, times, contacts, interventions and progress with the treatments explicitly documented. This enabled me to examine all records in a chronological order. Moreover, diagnosis are also entered into the record describing: 1) the main condition treated or (being) investigated during the relevant episode of healthcare, and 2) where there is no definitive diagnosis, the main symptom, abnormal findings or presenting problem (i.e. for the main condition being investigated).

2.3.5.2. General Practitioner (GP)

To trace those patients who dropped out from the services prematurely or were discharged from psychiatric care, I contacted their last known General Practitioners (GPs) via mail. The contact details of the last known GPs were obtained from the EPCRs. The letters sent included the following information: 1) details of the study, such as the name of the study, ethnic approval number and who to contact if more information/clarification was required; 3) the purpose of the contact; and 3) a short questionnaire the primary purpose of which was to explore the patients general state of health, whether the patient was still registered with the practice, and if so, requesting the GP to provide the patient's the most recent contact details. A reply slip and stamped addressed envelope were enclosed with the written request. A

copy of the letter sent to the GPs is included in Appendices (page 193); a copy of the short questionnaire that I included in the letter to the GPs is provided on page 180

2.3.5.3. Office for National Statistics (ONS)

All deaths and emigrations up to and including those that occurred during the final year of follow-up were identified by a case-tracing procedure with the Office for National Statistics (ONS) for England and Wales and the General Register Office (GRO) for Scotland. The Office for National Statistics (ONS) is the UK is largest independent producer of official statistics and is the recognised national statistical institute for the UK. It is responsible for collecting and publishing statistics related to the economy, population and society at national, regional and local levels. It also conducts the census in England and Wales every ten years. The patients' gender, date of birth, and last known address were used as identification variables for this case-tracing procedure.

2.3.6. Assessments at follow up

At follow-up, extensive information was collated across three course and outcome domains (*clinical*, *social*, and *service use*) from clinical records using the WHO Life Chart Schedule (LCS) extended version (WHO, 1992) [53, 237, 238]. This measure provides standardised retrospective assessments of patients' experience for the entire period of illness. The illness period was operationalised as the period from the first contact with mental health services for psychosis to the dates of the last assessment recorded in electronic notes. The LCS has been shown to be reliable for long-term follow-up assessment and adaptable across cultures[74, 238, 239]. A copy of the WHO LSC is included in the Appendices (page 196).

2.3.6.1. Social outcomes at follow-up

Using the LCS, I collected detailed information on sociodemographic characteristics of the patients that may be markers for overall social functioning and integration (i.e. housing, employment, relationships, education and social networks) for the entire follow up period as well as on last assessment at the end of the follow up period. Similarly, employing the LCS instrument I gathered information on substance use during the entire period of follow-up. For the latter outcome, patients were divided into those who reported ever having used illicit

drugs including cannabis (0); those who reported infrequent use (1); and those who had developed substance dependence (2). A similar approach was employed to coding history of alcohol consumption during the course of follow-up.

2.3.6.2. Clinical outcomes

2.3.6.2.1. Symptomatic Remission. Similarly to earlier work conducted in the same geographical region as my thesis [74, 240] and in line with the operational criteria proposed by Andreasen *et al* [154] using information extracted from clinical records I defined remission as an absence of overt psychotic symptoms (operationalized as a score of 2 or 3 on Rating Scale 2 in the SCAN; 0=absence, 1=symptom occurred, but fleeting, 2=symptom definitely present, 3=symptom present more or less continuously) for 6 months or longer. This measure of remission was not dependent on absence of non-psychotic symptoms (e.g. depressed mood, neurotic manifestations), nor if the patients were receiving a treatment with antipsychotic medications during remission.

2.3.6.2.2. Time to symptomatic remission. Time to remission was defined as the period from the date of first contact with mental health services for FEP to the date that the first 6-month period of remission started [241]. That is the date that overt psychotic symptoms were first absent and thereafter did not return for at least 6 months. This definition of time to remission is the same as that used in another FEP study from an overlapping geographical region [74].

2.3.6.2.3. Symptomatic Recovery. To be consistent with early study conducted in the same geographical region as this thesis [123] I defined symptomatic recovery as sustained symptomatic remission for consecutive 2 or more years.

2.3.6.2.4. Antipsychotic medication. Using patients' electronic case notes I extracted extensive information on antipsychotic medication use throughout patients' care at the Trust. This included the overall number of antipsychotic medication prescribed, names of individual antipsychotic medications, initiation/discontinuation dates and dose for each antipsychotic medication, and the primary reason for changing or discontinuing each antipsychotic medication. The dose for antipsychotic medications was recorded as a dose that proved to be therapeutic to the patients. This process of collecting information on antipsychotic

medication use was carried out from the first contact with mental health services for psychosis throughout the follow up period.

2.3.6.2.5. Antipsychotic medication adherence. Using the LCS and based on the notes recorded by the treating clinicians, I further assessed the patients' adherence to antipsychotic medications over the course of my follow up. This assessment was made on a three point scale ranging from 1 to 3 (1 [0=33%], 2 [33-67], and 3 [67-100%]) indicating the proportion of follow up period during which a patient regularly took antipsychotic medications as prescribed. These codes do not include non-adherence explicitly due to treatment intolerance; for example, if a patient did not take medications because of adverse effects, but once better tolerated medications were prescribed the compliance improved to 100% and remained so for the rest the follow up period , I coded them as "3 [67-100%]".

2.3.6.2.6. Definitions of treatment resistance (TR). Patients were defined as having TR if 1) they were treated with clozapine over the course of the five year follow up period; and 2) during the follow up period they showed little or no symptomatic improvement to two consecutive treatments with antipsychotic medications of adequate dose and duration (at least 6 weeks), but were not commenced on clozapine [192]. The adequate daily dose of antipsychotic medication was defined according to a daily dose of at least 400mg chlorpromazine equivalents [242]. Patients who met either or both of these two criteria for treatment resistance were defined as such. I only included as TR cases those patients, who failed to respond, and not those who were intolerant to the prescribed antipsychotic medications or those who self-discontinued medication.

2.3.6.2.7. "Early-resistance" (E-TR) and "Late-resistance" (L-TR). Those who met the criteria for TR were divided into two subgroups: 1) "early-resistance" (E-TR) group which included FEP patients who met criteria for TR and who did not experience a symptomatic remission from the time of the first presentation to mental health services; and 2) "late--resistance" (L-TR) encompassed FEP patients who had experienced a response to antipsychotics and attained symptomatic remission (of at least 6 months duration), but at a later stage failed to respond to the ongoing use of non-clozapine antipsychotics, ultimately meeting the criteria for TR.

2.3.6.2.8. The Global Assessment of Functioning (GAF) at the end of follow up. Similarly to baseline, the GAF assessing both symptoms and functioning was used to measure the

overall illness severity at the end of the 5-year follow-up using the clinical notes. There were excellent intra-class correlations when rating GAF symptoms (GAF-S) from clinical records (intra-class correlation (ICC)>0.90). Further, GAF-S scores collected from clinical records compared to GAF-S scored via face to face interview showed high comparability (ICC=0.81). Copies of GAF symptoms and disability scales are presented in Appendices (pages 191 and 192).

2.3.6.3. Services utilisation

Utilising the LCS extended version [53, 74, 237, 238] and excluding the admission made on the first contact for psychosis, I collected detailed information on circumstances of re-admissions including the use of Mental Health Act (MHA) legislation and the involvement of police at the time of, or shortly before, hospital re-admission. Excluding the first hospital admission on first contact with mental health services for psychosis, *the cumulative number of re-admissions* was obtained by summing hospital admissions throughout the follow up period. To calculate a cumulate stay as an inpatient during the entire follow up period for each patient I extracted information on the date of admission and date of discharge. The days spent as an inpatient during each hospital admission were subsequently calculated and then summed up them together. A cumulative number of outpatients (or community) mental health services throughout the entire follow up period was derived in a similar manner as it was conducted for the hospital re-admissions. The types of outpatient/community services each patient was referred to were categorised into two main groups: 1) “regular” community services meaning contact with the services at intervals of less or equal to one months for prescription or monitoring medications and general well-being; and 2) “intensive” community services encompassing all individual requiring contact with the assertive outreach services and/or acute home treatment teams/crisis intervention services.

2.3.7. Statistical analyses

All analyses in the present thesis were conducted in STATA release 12 or 14 (STATACorp LP, USA). All statistical tests were 2-sided, and a *p*-value ≤0.05 was considered statistically significant.

2.3.7.1. Descriptive statistics

I described the primary outcomes using frequencies, percentages, mean and standard deviations or median with interquartile ranges (IQR). Cumulative survival curves were constructed by using Kaplan–Meier estimates.

2.3.7.2. Comparative statistics

Comparisons between the groups were conducted using x^2 tests or *Fisher's* exact test for categorical variables and *t*-test (or Mann-Whitney *U* test) and/or ANOVA (or Kruskal–Wallis one-way analysis of variance) for continuous variables; and range and rank test χ^2 for the count data.

2.3.7.3. Confirmatory factor analysis (CFA)[3]

Using psychotic symptoms as measured by PANSS, I conducted CFA to evaluate the statistical fit [243] of the Wallwork/Fortgang's five factor model of psychosis [26] in patients with FEP. This model included the *positive* (i.e., P1, P3, P5, G9), *negative* (i.e., N1, N2, N3, N4, N6 and G7), *disorganised/concrete* (i.e., P2, N5, G11), *excited* (i.e., P4, P7, G8 and G14), and *depressed* (i.e., G2, G3 and G6) factors. These factors were entered as latent variables in the CFA and the PANSS items were entered as observed variables. The Goodness-of-Fit Index (GFI) statistics were used to determine the adequacy of fit of the model. These included the comparative fit index (CFI; values greater than 0.90 indicate good model fit), the root mean square error of approximation (RMSEA; values less than 0.06 indicate good model fit), and the standardised root mean square residual (SRMR; values less than 0.08 indicate good model fit) [243]. To improve the model fit I further incorporated the correlated measurement errors into the model based on significantly correlated residuals as indicated by modification indices [15]. Following CFA, factor scores for each of the five symptom dimensions were calculated for each patient using STATA's 'predict' post-estimation command.

[3] These statistical methods were reported in the paper: Ajnakina O, Trotta A, Oakley-Hannibal E, Di Forti M, Stilo SA, Kolliakou A, et al. (2015). Impact of childhood adversities on specific symptom dimensions in first-episode psychosis. *Psychological Medicine* **46**, 317-26

2.3.7.4. Association analyses

In this subsection I provide a concise overview of what association analyses I used to test my hypotheses (where appropriate). The association analyses in this thesis were specific to each hypothesis and thus the rational and method of selecting the appropriate association analyses varied from study to study. Therefore, I have provided the detailed description of these analyses under methods section in each study.

- To investigate the impact of psychosis symptom dimensions and baseline diagnostic categories on the time to first remission, I utilised an accelerated failure time model for right censored data (Chapter 3, Study 2).
- To examine associations between the outcomes and ethnic groups, for count data I applied Poisson regression or Negative binomial regression, depending on the distribution of the outcomes (Chapter 4, Study 3).
- I utilised the Cox proportional-hazards regression to model the binary outcomes (Chapter 4, Study 3).
- I employed Penalised logistic regression to analyse the relationship between the baseline predictors for treatment resistance status established by the end of the 5-year follow up period (Chapter 6, Study 4).

2.4. Statement of contribution to the investigations

This is to confirm that the work presented in the thesis is my own carried out under the supervision of Prof Anthony David (Chapter 3, Study 1) and Prof Sir Robin M Murray (Chapters 1-8). As part of the Study 1, my main contributions to the EU-GEI study is data collection on socio-demographic and clinical characteristics, and pathways to care from the CRIS system for *n*=551 patients using the MRC Socio-demographic Schedule (modified version). Although I collected information for *n*=551 patients, in the Study 1 I report data for *n*=338 patients only.

As part of Studies 2, 3 and 4, my main contributions to the GAP study involve collecting the extensive information on three domains-clinical, social and service uses using electronic case notes for *n*=367 (82% of *n*=449 original GAP sample) patients over the first five years after first contact with mental health services for psychosis. I further established the

whereabouts, deaths and emigration status, either through the electric patient notes, contacting their general practitioners or the ONS for England and Wales and the GRO for Scotland, for 89.7% of the original GAP study at the end of the 5-year follow up. *Exceptions include*: all the baseline data such as PANSS score and socio-demographic characteristics that I used in studies 2, 3 and 4 were collected by GAP researchers at the time of the start of the GAP study. I have created and organised all variables corresponding to the EU-GEI and GAP studies using SPSS v 22 and STATA v12/14. In terms of statistical analyses, I was responsible for researching the most appropriate and robust statistical methods to test my hypotheses that I reported in this thesis.

CHAPTER 3 STUDY 1

First-Episode Psychosis in South London: looking back at use of prodromal services

3.1. Introduction

In this study I set out to identify the proportion of patients with a FEP who had first presented to the 'at risk' services with the ARMS and who, by definition, subsequently transitioned to FEP (i.e., PROD group), and characterise this group in terms of their clinical and socio-demographic characteristics. Moreover, I sought to test whether there were significant differences in clinical presentation, socio-demographic characteristics and pathways to care between the PROD and FEP-C groups (the latter group encompassed all those patients without prior contact with the prodromal service before their first contact with the early intervention services for FEP). I hypothesised that the interval between the first onset of psychosis symptoms and initiation of treatment will be shorter in the PROD group compared to FEP-C group. To answer the additional question of whether those referred to the ARMS services who were already experiencing a FEP at the time of the first contact (i.e., FEP-P group) [28, 244] were different from the standard first episode populations (perhaps because of factors related to help-seeking behaviours), I further compared the clinical presentation, socio-demographic characteristics and pathways to care between FEP-P and FEP-C groups.

3.2. Methods

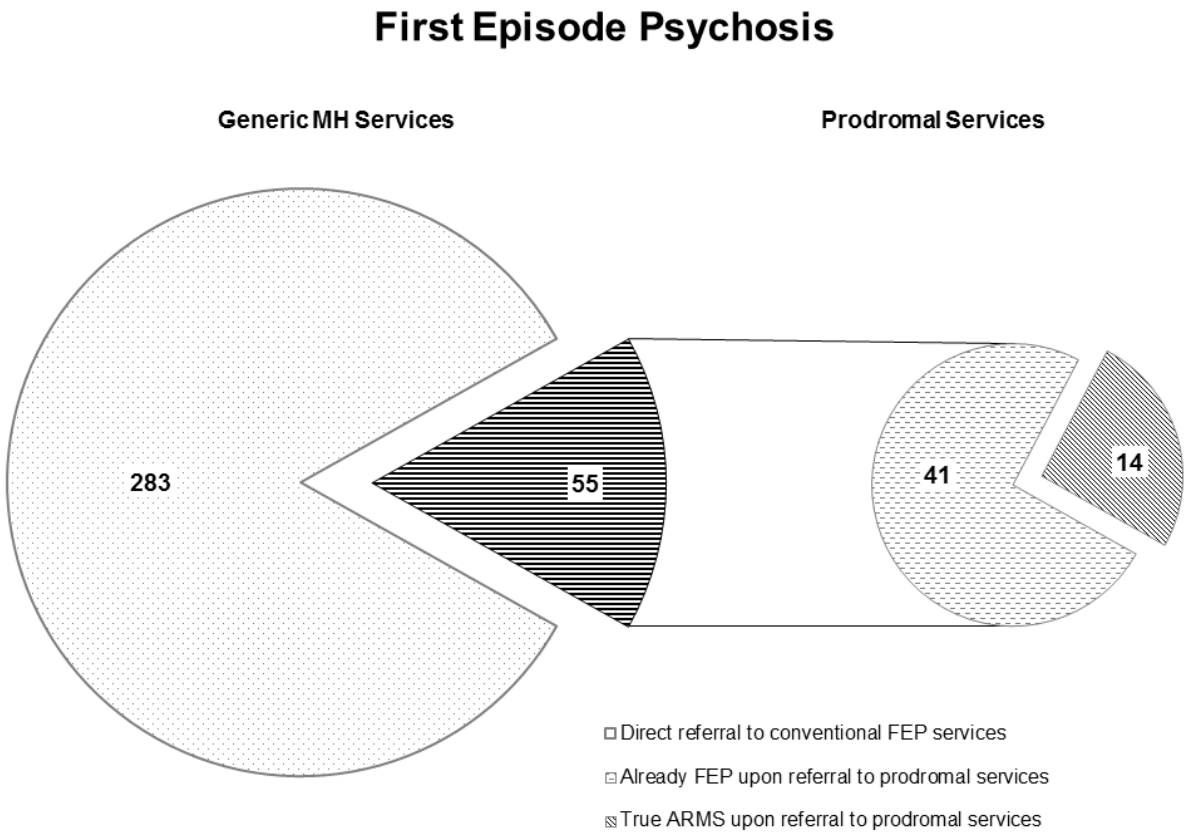
The participants aged ≤37 years old used in this study were recruited as part of the EU-GEI study. I compared sociodemographic characteristics, clinical presentation, DUP and pathways to care in patients attending the Outreach and Support in South London Service (OASIS), a specialised community mental health service for people with the ARMS for psychosis [28, 37], (i.e., *PROD group*) with FEP patients without a prior contact with the OASIS services before their first contact with the early intervention services for FEP (*FEP-C group*). I additionally derived a third group of patients who were found to be already experiencing their FEP at the time of first contact with the OASIS (i.e., *FEP-P group*). All patients were identified within a tightly defined catchment area catered for by the SLaM Trust. For more detailed description of the methods (refer to Chapter 2, section 2.2.2, page 66)

3.3. Results

3.3.1. Sample characteristics

The information on identification of the groups is illustrated in the **Figure 4**. Between 2010 and 2012, there were 338 referrals for first onset psychosis within the Southwark and Lambeth boroughs served by the Trust. Of these, 283 (83.7%) were referred to conventional mental health services for FEP without prior contact with the prodromal clinic (i.e., FEP-C group). The remaining *n*=55 (16.3% of *n*=338) FEP patients had been in contact with the prodromal clinic before making the transition to FEP. Of these, *n*=14 (25.5% of *n*=55 and 4.1% of *n*=338 FEP cases) were true ARMS patients and who subsequently transitioned to FEP (i.e., PROD group) and *n*=41 (74.5% of *n*=55 and 12.1% of *n*=338) were already psychotic at the time of their contact with the ARMS team (i.e., FEP-P group).

Figure 4. *Information on identification of the FEP-C, FEP-P and PROD groups*



FEP-C group, first episode psychosis patients without a prior contact with prodromal teams; FEP-P group, patients who were already in a first episode psychosis upon referral to the prodromal services; PROD, first episode psychosis patients with (prior contact with the prodomal services

3.3.2. Socio-demographic characteristics: FEP-C vs PROD groups

Comparisons in socio-demographic characteristics between the FEP-C and PROD groups at the time of first contact with mental health services are presented in **Table 4**. At the time of first contact, the FEP-C group was older ($mean_{years}$=27.9, s.d.=5.5) than the PROD group ($mean_{years}$ =24.2, s.d.=6.0) (*t*=2.46, df=295, *P*=0.01). A higher proportion of the PROD group (83.3%) was born in the UK compared to the FEP-C group (47% of *n*=234) (x^2=6.14, df=1, *P*=0.01). There were no other statistically significant differences between these groups.

Table 4. *Comparisons in socio-demographic characteristics between first episode psychosis patients with (i.e., PROD group) and without (i.e., FEP-C group) prior contact with the prodomal services in South London*

Socio-demographic characteristics	FEP-C (*n*=283; 83.7%)	PROD (*n*=14; 4.1%)	Statistics		
	Mean(s.d.)/*n*(%)	Mean(s.d.)/*n*(%)	Test statistics	df	*P*-value
Age $_{years}$	27.9 (5.5)	24.2 (6.0)	2.46	295	0.01
Gender					
Female	124 (43.8)	5 (35.7)	0.36	1	0.60
Male	159 (56.2)	9 (64.3)			
Ethnicity					
White	98 (35.1)	7 (53.8)	2.65	2	0.29
Black	126 (45.2)	3 (23.1)			
Other	55 (19.7)	3 (23.1)			
Country of birth					
UK	124 (46.8)	10 (83.3)	6.14	1	0.01
Not in the UK	141 (53.2)	2 (16.7)			
Education					
School	111 (55.2)	8 (72.7)	1.30	1	0.35
A-Level, or above	90 (44.8)	3 (27.3)			
Employment status					
Unemployed	172 (64.7)	7 (50.0)	1.24	1	0.27
Employed	94 (35.3)	7 (50.0)			
Marital status					
Not in stable relationship	207 (75.3)	7 (53.9)	2.98	1	0.10
Married/stable relationship	68 (24.7)	6 (46.1)			
Living arrangements					
Alone	74 (27.0)	1 (7.1)	4.08	2	0.15
Partner/family	125 (45.6)	10 (71.4)			
No stable accommodation	75 (27.4)	3 (21.4)			
Cannabis use					
No	118 (50.2)	4 (30.8)	1.86	1	0.26
Yes	117 (49.8)	9 (69.2)			

FEP-C-patients who present to conventional FEP services; PROD–prodromal patients who presented to prodromal services; IQR, 25th and 75th Percentiles range; s.d, standard deviation; df, degree of freedom

3.3.3. Clinical presentation and pathways to care: FEP-C vs PROD groups

Comparisons in clinical presentation and pathways to care between the FEP-C and PROD groups at the time of first contact with mental health services are presented in **Table 5**. DUP was highly skewed; the median length of DUP in the PROD group was 19 days (IQR=6-40); whereas for the FEP-C group the median of DUP was 86 days (IQR=13-368). Although this looks different, it was not significantly different (analysis after log transformation), presumably because of small numbers in the PROD group. Seventy three percent of the PROD group (*n*=8/11) and 36% of the FEP-C group had an insidious mode onset of first psychotic symptoms (x^2=6.67, df=2, *p*=0.05). The pathways to care for FEP were significantly different between the groups (x^2=8.72, df=3, *p*=0.02): 45% (*n*=124/274) of the FEP-C group made their first contact with mental health services via emergency services and 18% of this group were referred by criminal justice system. In contrast, around 77% of the PROD group were referred to the prodromal clinic by either GP or other health professionals.

Table 5. *Comparisons in clinical presentation characteristics, and pathways to care between first episode psychosis patients with (i.e., PROD group) and without (i.e., FEP-C group) prior contact with the prodomal services in South London*

Clinical presentation and pathways to care	FEP-C (*n*=283; 83.7%)	PROD (*n*=14; 4.1%)	Statistics		
	Median (IQR)/*n*(%)	Median (IQR)/*n*(%)	Test statistics	df	*P*-value
DUP $_{days}$	86 (13-368)	19 (6-40)	1.35	219	0.18
Source of referral					
General Practitioner	67 (24.5)	6 (46.2)	8.72[a]	3	0.02
Emergency services	124 (45.3)	2 (15.4)			
Health & social worker	34 (12.4)	4 (30.8)			
Criminal justice agency	49 (17.9)	1 (7.7)			
Mode of onset					
Acute	121 (43.7)	2 (27.3)	6.67	2	0.05
Gradual	56 (20.2)	-			
Insidious	100 (36.1)	8 (72.7)			

FEP-C-patients who present to conventional FEP services; PROD–prodromal patients who presented to prodromal services; DUP, duration of untreated psychosis; GP, general practitioner; IQR, 25th and 75th Percentiles range; s.d, standard deviation; df, degree of freedom

[a] The analyses were conducted using the logarithmic-transformed values

3.3.4. Socio-demographic characteristics, DUP and pathways to care: FEP-C vs FEP-P groups

Comparisons in socio-demographic and clinical characteristics and pathways to care between the FEP-C and FEP-P groups at the time of first contact with mental health services are presented in **Table 6**. At the time of first contact the ARMS team, *n*=41 (74.5% *n*=55 FEP patients who had a prior contact the ARMS services) were already experiencing a full psychotic episode (i.e., FEP-P). The FEP-P group was younger ($mean_{years}$=24.7, s.d.=4.4) than the FEP-C group ($mean_{year}$=27.9, s.d.=5.4) (*t*=3.56, df=322, *p*<0.001). A higher proportion of the FEP-P group lived with members of their family or partners (63% of *n*=41) compared to the FEP-C group (46% of *n*=274) (x^2=6.77, df=2, *p*=0.03). Further, the pathways to care differed between the groups (x^2=9.94, df=3, *p*=0.02); 46% of the FEP-P group were referred to mental health services by their local GPs, while 45% of the FEP-C group was referred by emergency services; 17.9% of the FEP-C group, compared to 7.7% of the FEP-P group, came in contact with mental health services via criminal justice agency

Table 6. *Comparisons in socio-demographic characteristics, clinical presentation and pathways to care between first episode psychosis patients without prior contact the prodromal teams (i.e., FEP-C group) and those who were already in a first episode psychosis upon referral to the prodromal services (i.e., FEP-P group) in South London*

Presentation at first contact with mental health services	FEP-C (*n*=283; 83.7%)	FEP-P (***n***=41; 12.4%)	Statistics		
Socio-demographic characteristics	Mean(s.d.)/*n*(%)	Mean(s.d.)/*n*(%)	Test statistics	d.f.	*P*-value
Age	27.9 (5.4)	24.7 (4.4)	3.56	322	<0.001
Gender					
Female	124 (43.8)	17 (40.5)	0.08	1	0.78
Male	159 (56.2)	24 (59.5)			
Ethnicity					
White	98 (35.1)	15 (36.6)	0.16	2	0.92
Black	126 (45.2)	19 (46.3)			
Other	55 (19.7)	7 (17.1)			
Country of birth					
UK	124 (46.8)	23 (62.2)	3.01	1	0.08
Not in the UK	141 (53.2)	14 (37.8)			
Education					
School	111 (55.2)	13 (39.4)	2.85	1	0.09
A-Level or above	90 (44.8)	20 (60.6)			
Employment status					
Unemployed	172 (64.7)	26 (63.4)	0.02	1	0.88
Employed	94 (35.3)	15 (36.6)			
Marital status					
Not in stable relationship	205 (75.1)	32 (80.0)	0.46	1	0.56
Married/stable relationship	68 (24.9)	8 (20.0)			
Living arrangements					
Alone	74 (27.0)	11 (26.8)	6.77	2	0.03
Partner/family	125 (45.6)	26 (63.4)			
No stable accommodation	75 (27.4)	4 (9.8)			
Cannabis use					
No	118 (50.2)	19 (51.3)	0.02	1	0.90
Yes	117 (49.8)	18 (48.7)			
DUP days Median(IQR)	86 (13-368)	104.5 (52-387)	-0.77[a]	253	0.44
Source of referral					
GP	67 (24.5)	18 (46.2)	9.94	3	0.02
Emergency services	124 (45.3)	12 (30.8)			
Health & social worker	34 (12.4)	6 (15.4)			
Criminal justice agency	49 (17.9)	3 (7.7)			
Mode of onset					
Acute	121 (43.7)	15 (36.6)	1.83	2	0.40
Gradual	56 (20.2)	12 (29.3)			
Insidious	100 (36.1)	14 (34.1)			

FEP-C, who present to conventional FEP services; FEP-P, FEP referrals with prior contact with prodromal services; DUP, duration of untreated psychosis; GP, general practitioner; IQR, 25th and 75th Percentiles range; s.d, standard deviation; df, degree of freedom; [a] The analyses were conducted using the logarithmic-transformed values

3.4. Discussion

In this study I showed that 4.1% of patients presenting to mental health services with FEP had previously presented to the ARMS services during the prodromal phase of psychosis and subsequently transitioned to a full-blown psychotic disorder. Although the ARMS services are well-known locally, it may be that recognising pre-psychotic cases is much more difficult than might be assumed [245]. It is also feasible that a larger proportion of FEP cases have an acute onset without a clear prodrome than is commonly appreciated. The task of effectively detecting true at risk cases based on referrals and help-seeking rather than epidemiological surveys is clearly challenging especially given the lack of sensitive and specific biomarkers indicative of the prodromal phase of psychosis [246, 247]. If these figures are replicated in other similar settings with similar prodromal services, it will suggest that the promise of early detection of those at high risk for transition to a psychotic disorder with the aim of large scale primary prevention is still some way off. Even if effective, safe, acceptable and economical interventions were readily available we are not yet in a position to apply them in a way which could make anything but the smallest impact on the incidence of psychosis.

3.4.1. How could we increase the number of patients coming to ARMS services?

I found that around 77% of all referrals to the ARMS services were made by health professionals such as local GPs and other health workers. Clearly this pathway leaves out young individuals developing psychosis who do not seek help [248, 249] or are not registered with GPs. Similarly, migrants may be less likely to be registered with GPs and may have less trusting attitudes toward mental health professionals [250]. Indeed, I found that a greater proportion of prodromal patients who came in contact with the ARMS services were born in the UK. Further, the likelihood of help-seeking is influenced by the mode of onset of psychotic symptoms [251]. Previous studies showed that patients in less symptomatic states were more likely to seek help from their GPs [251]. Considering that 44% of all the FEP cases had an acute onset of psychotic symptoms, it is not surprising that many would not have sought help via GPs and thus accessed the ARMS services. The age of first contact was younger in FEP patients who had first presented to the ARMS services and subsequently transitioned to psychotic disorder than in the FEP group without prior contact with prodromal services. This shows that the ARMS services are successful in reaching out to younger clients; though it also may reflect an artefact of the age limit imposed by the services.

Moreover, the DUP was not different between the groups. Nevertheless, it is possible that treatment delay could have been even longer for these individuals had it not been for the presence of the ARMS services.

Additionally, I found that around 75% of all referrals to the ARMS services were already experiencing their first episode psychosis at the time of the contact with the prodromal team. Although this supports the notion that the ARMS services are successful in detecting FEP patients who are in turn promptly referred to more appropriate early intervention services, the results of the study do not suggest that the ARMS services provide additional functions by detecting individuals with FEP who otherwise would not have had access to mental health services.

3.4.2. Methodological considerations

The results of the present study should be interpreted in light of methodological limitations. Although the SLaM BRC Case Register, which was the primary source of information for the present study, has a near 100% clinical coverage in its boroughs[221], it is still feasible that some of the patients might have sought or purchased mental healthcare elsewhere for a psychotic disorder and thus would not have been registered in the SLaM BRC Case Register, nor included in the present study. It may be argued that extracting information from clinical records may not always produce reliable data. For example, for the purposes of determining DUP from clinical records, treating clinicians might not always have recorded in the notes when psychosis symptoms began and their magnitude. The quality and completeness of information recorded in the electronic notes for each case inevitably varied and this may have introduced some bias. Finally, the data relating to living circumstances, relationship status and employment provide crude proxies for social networks and as such they can only hint at the potential role of social contexts and networks in influencing the pathway to care.

3.5. Summary and concluding remarks

Little is known about patients with a FEP who had first presented to prodromal services with ARMS and who subsequently transitioned to psychotic disorder. I investigated the differences between FEP patients with and without a prior contact with the ARMS services

within a tightly defined catchment area in South London. In this study, employing 338 FEP patients aged up to 35 plus 2 years who presented to the mental health services between 2010 and 2012, I found that a small fraction of individuals (4.1%) who present with FEP to the main secondary mental health provider had previously been in contact with the ARMS services and made a subsequent transition to a psychotic disorder. Although my results were suggestive that the ARMS services in South London have been successful in reducing the delays from the first onset of psychotic symptoms to the initiation of appropriate treatments, the overall difference between the groups did not reach the accepted level of statistical significance. The ARMS services indeed performed a useful service in providing an extra pathway for patients who were already psychotic; yet the overall findings indicate that such services are unlikely to be in a position to prevent all but a few at-risk individuals transitioning to a FEP even if effective preventative treatments were available.

CHAPTER 4 STUDY 2

Symptom dimensions versus DSM-IV diagnostic categories as predictors of time to first remission in first-episode psychosis

4.1. Introduction

In this study, I compared the utility of psychosis symptom dimensions derived using the Wallwork/Fortgang five-factor model [26] with conventional diagnostic categories to predict time to remission in a sample of patients with FEP. I hypothesised that the symptom dimensions would provide a more accurate prediction of time to first remission compared to the diagnostic categories. Building on previous research which highlighted that combining dimensional measures with categorical diagnoses is more informative in determining the causes of psychosis than considering them separately[218], I further tested whether combining symptoms dimensions with categorical diagnoses would lead to a more robust model for predicating time to first remission.

4.2. Methods

4.2.1. Sample

The original GAP sample comprised *n*=339 FEP cases; of these Positive and Negative Syndrome Scale (PANSS [234]) scores were available for *n*=236 cases (69.6% of the original GAP sample). This subsample with PANSS ratings did not differ significantly from the full GAP sample in terms of gender, age, ethnicity and baseline diagnosis (**Table 7**). For the purposes of this study the baseline diagnoses were grouped using DSM-IV codes into schizophrenia (295), schizophreniform disorder (295.40), and affective psychoses (296, 296.24, 296.44). Because the diagnosis of schizoaffective disorder does not have a clear construct, as it is a mixture of schizophrenia and affective symptoms,[252] and a relatively small sample of patients had this diagnosis, I combined schizoaffective disorder with the other psychoses in the analyses and labelled this group as 'other psychoses' (295.70, 297.1, 298.9).

The self-reported ethnicities were categorised into three broad ethnic groups: White (all white groups), Black (all black groups) and Other (mixed and all other ethnic groups).

4.2.2 Data at follow up

Approximately 4 years after first contact with mental health services for psychosis, 81% of this subsample (*n*=191/236) was successfully traced. Therefore, the data presented here are based on these *n*=191 cases (56.3% of the 339 original GAP cases).

For detailed description of definitions of remission and time to remission please refer to Chapter 2, sections 2.3.6.2.1 and 2.3.6.2.2., page 75. For the detail description of methods used to derive the five symptom dimensions used in this study please refer to Chapter 2, section 2.3.7.3., page 78.

Table 7. *Comparisons of demographic and clinical characteristics between patients with and without PANSS data available at baseline in the full GAP sample*

Baseline characteristics	Completed PANSS (*n*=236; 69.6%)		Not completed (*n*=103; 30.4%)		Test statistic		
	Mean/*n*	sd/%	Mean/*n*	sd/%	t/x^2	df	*p*
Age at first contact	28.9	9.1	30.6	10.2	1.50	325	0.13
Gender							
Female	45	38.8	77	35.2	0.43	1	0.29
Male	71	61.2	142	64.8			
Ethnicity							
White (all categories)	80	43.5	80	44.2	0.02	1	0.89
Black (all categories)	104	56.5	101	55.8			
Diagnosis							
Schizophrenia	59	26.1	26	27.4	0.36	*3*	0.95
Schizophreniform	65	28.8	25	26.3			
Affective Psychoses	52	23.0	24	25.3			
Other Psychoses	50	22.1	20	21.0			

df, degrees of freedom. GAP, Genetics and Psychosis study. PANSS, Positive and Negative Syndrome Scale. sd, standard deviation.

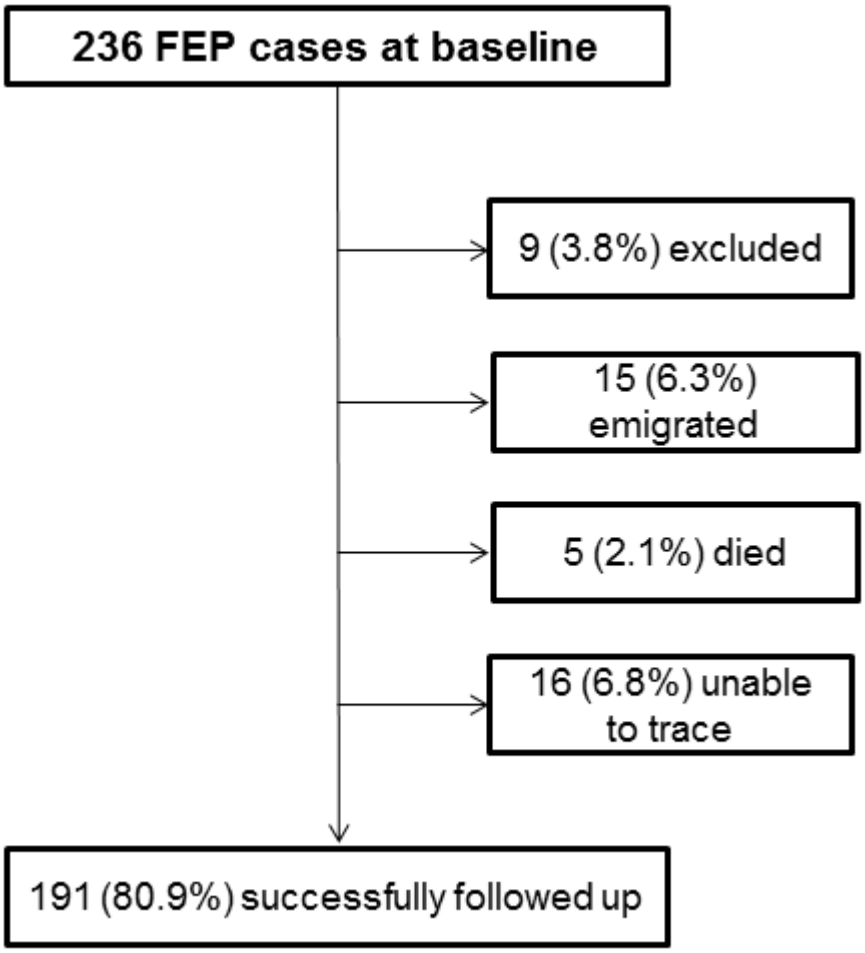
The tracing procedure is outlined in **Figure 5**. During the first four years of follow-up, of all FEP cases included in the original GAP study with PANSS ratings available, *n*=15 (6.3%) emigrated, *n*=5 (2.1%) had died, and *n*=9 (3.8%) were excluded as these patient did not have information on follow up and their contact details were not available at baseline to enable to me trace them either via their GP or ONS/GRO tracing procedures. I was unable to trace the remaining 16 (6.8%) patients via electronic records. Ultimately, I successfully traced 93.2% of my original sample and the full information at follow-up was available for 80.9% (*n*=191/236) of patients. Those who had died or were excluded tended to be significantly older; there were no differences in gender, ethnicity or diagnosis at baseline by administrative outcome (**Table 8**).

Table 8. *Baseline demographic characteristics and diagnosis by administrative outcome*

Baseline characteristics	Total		Followed up		Unable to trace		Abroad		Died		Excluded		Test statistic		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	t/x^2	df	*p*
Sample with PANSS ratings	236	100	191	81.9	16	6.8	15	6.3	5	2.1	9	3.8			
Gender															
Female	80	34.8	68	35.6	5	31.2	5	33.3	2	40.0	-	-	1.82	4	0.88
Male	150	65.2	123	64.4			10	66.7	3	60.0	3	100			
Age $_{years}$ Mean (s.d.)	28.6	9.0	28.2	8.3	30.9	11.6	26.3	6.8	37.6	17.2	38.3	18.8	2.79	227	0.03
Ethnicity															
White (all categories)	81	34.9	66	34.2	7	43.7	4	26.7	3	60.0	1	*33.3*	4.09	8	0.85
Black (all categories)	94	40.5	77	39.9	6	37.5	8	53.3	2	40.0	1	33.3			
Other	57	24.6	50	25.9	3	18.8	3	20.0	-	-	1	33.3			
Diagnosis															
Schizophrenia	59	26.5	53	28.5	3	18.8	1	6.7	2	50.0	-	-	9.09	12	0.62
Schizophreniform	65	29.2	52	28.0	5	31.2	6	40.0	1	25.0	1	50.0			
Affective Psychoses	51	22.9	43	23.1	3	18.7	5	33.3	-		-				
Other Psychoses	48	21.5	38	20.4	5	21.3	3	20.0	1	25.0	1	50.0			

df, degrees of freedom. PANSS, Positive and Negative Syndrome Scale. SD, standard deviation

Figure 5. *Flow chart documenting how n=191 psychosis patients were traced and administrative outcomes four years after first contact with mental health services for a first episode of psychosis (FEP).*



4.2.3. Data Analyses

Detailed description of the methods employed to conduct the confirmatory factor analyses are provided in the Chapter 2, section 2.3.7.3., page 78.

4.2.3.1. Survival analyses. To better understand the impact of baseline factors on the time to first remission, I utilised an accelerated failure time model (AFT) for right censored data. The main differences between the AFT and Cox regression analyses is that while Cox regression model assumes that the effect of a covariate is to multiply the hazard by some constant, an AFT model assumes that the effect of a covariate is to accelerate or decelerate the life course of illness by some constant [253]. The best-fitting parametric model was identified by comparing the Bayesian Information Criterion (BIC) between the exponential, Weibull, lognormal and gamma models, not including confounders. The BIC quantifies the overall uncertainty associated with the data and the model parameters with the smaller values being indicative of a better model fit. The results of these analyses showed that the model with Gamma distribution was the most appropriate for my analyses.

4.2.3.2. Converting parameter coefficients into weeks to remission. The parameter coefficients in the AFT model were converted into differences in weeks in time to remission through the equation (e^{β} x median time of follow-up (i.e., 208.4 weeks)) [254]. For continuous variables, the beta-coefficient indicates the time difference measured in weeks in time to remission associated with a 1-unit increment in the explanatory variable. For categorical variables, this value indicates the time difference measured in weeks in time to remission by comparing 1 level with the reference level. Positive values denote longer time to remission; whereas negative values indicate shorter time to remission [254].

4.2.3.3. Identifying potential confounding variables. I examined variables collected at baseline (i.e., age at first contact with mental health services, relationship and employment status, living arrangements, educational attainments, DUP, and illicit substance use) and during the follow-up (i.e., medication adherence, relationship and employment status, living arrangements and illicit substance use) by conducting univariate analysis with time to remission as the dependent variable. The covariates with *p*-values of <0.20 were considered for my multivariate model. I eliminated the variables with the largest *p*-values individually until all the remaining variables had a *p*-value of <0.05. This procedure highlighted age at

first contact, DUP and illicit substance use during the follow-up period as important confounding factors. Although the variable that measured the compliance with antipsychotic medications over the course of follow-up did not meet this inclusion criteria for the final model, based on the evidence indicating that this was an important confounding factors for time to remission [217] I included this additional variable in my final analyses.

4.2.3.4. Testing model fit. I tested different models, each including either symptom dimensions or diagnostic categories, or combination of both, as the main predictors of time to first remission after first contact with mental health services for psychosis. Similarly to selection of the best distribution of the AFT model, I used the BIC to test the model fit. The model with the lowest BIC score fits the data best. To compare models, I calculated $_{\Delta}$BIC which was defined as the model minus the model with the lowest BIC score [255]. Therefore, the best model will have a $_{\Delta}$BIC score of 0. Models >4 units away from the best model ($_{\Delta}$BIC>4) are considered to be significantly inferior compared to the best model (i.e., the best model will have a BIC=0); whereas the models that have more than 10 units away from the best fit model ($_{\Delta}$BIC>10) are considered to have little or no support from the data [255].

4.3. Results

4.3.1. Core analytic sample

Demographic characteristics for the core analytic sample of *n*=191 cases and remission of psychosis over four-year follow-up are presented in **Table 9**. An average of four years after first contact with mental health services for psychosis ($mean_{years}$=4.4, s.d.=1.7; 832 person years), I successfully traced *n*=191 (80.9% of *n*=236) patients using their electronic notes. The mean age at first contact was 28.6 years (s.d.=9.0); nearly two-thirds (64.4%) of the sample were men and 46.1% were of White ethnicity. Thirty-eight percent of the sample had a diagnosis of schizophrenia and 19% were diagnosed with manic psychosis. Further, 67% of my sample was recruited from inpatient services and 96% were on antipsychotic medication at the time of study entry.

Table 9. *Baseline demographic characteristics for n=191 first episode psychosis patients with PANSS data and who were successfully followed up over four-year follow-up from first presentation to mental health services*

Baseline sample characteristics and remission at follow-up	Total sample *n*=191	
	Mean/*n*	s.d./%
Age $_{years}$	28.6	9.0
Gender		
Female	68	35.6
Male	123	64.4
Ethnicity		
White (all groups)	65	46.1
Black (all groups)	46	32.6
Other	30	21.3
Diagnosis		
Schizophrenia	53	28.5
Schizophreniform	52	28.0
Affective Psychoses	43	23.1
Other Psychoses	38	20.4
On antipsychotic medication at study entry	184	96.3
DUP $_{days}$	35.0	118.6
Years of follow-up	4.4	1.8
Median (IQR)	4	3-5
Rate of remission	112	60.2
Time to remission $_{weeks}$	18.3	26.0
Median (IQR)	8	5-20

DUP, duration of untreated psychosis; IQR, Interquartile range; s.d., standard deviation

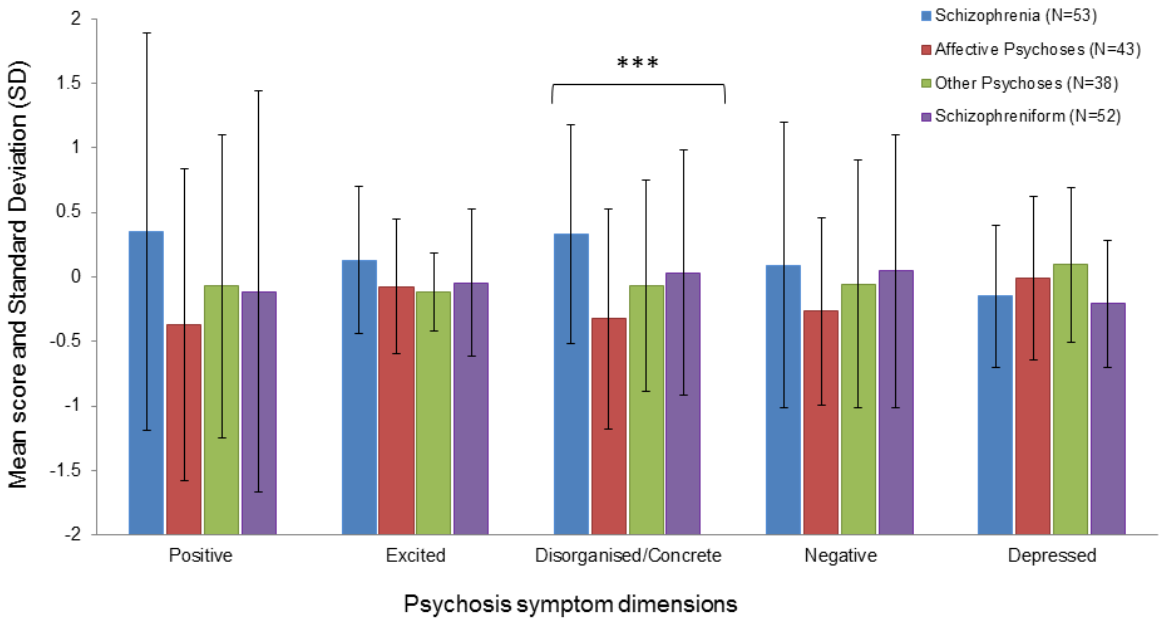
4.3.2. Confirmatory factor analysis [4]

CFA was conducted in the current sample with the Wallwork/Fortgang five-factor model of PANSS items [26]. When the correlated residuals (i.e., measurement errors) were not introduced into the model, the results of CFA indicated a poor model fit: CFI=0.767, RMSEA=0.101 (90% CI 0.092-0.111) and SRMR=0.111. However, once significantly correlated residuals were incorporated into the model, the CFA produced an excellent fit of the model: CFI=0.959, RMSEA=0.052 (90% CI 0.037-0.067) and SRMR=0.071.

The mean symptom dimension scores at entry to mental health services by diagnostic categories are illustrated in **Figure 6**. Although five symptom dimensions are evident across all diagnostic categories, patients with the baseline diagnosis of schizophrenia scored more highly on the disorganised/concrete symptom dimension compared to those with manic and other psychotic disorders (F=4.63, df=185, p=0.004).

[4] These results have been published in Ajnakina O, Trotta A, Oakley-Hannibal E, Di Forti M, Stilo SA, Kolliakou A, et al. (2015). Impact of childhood adversities on specific symptom dimensions in first-episode psychosis. *Psychological Medicine.* **46**, 317-26

Figure 6. *Five psychosis symptom dimension scores by traditional DSM-IV diagnostic categories*



Graphs display the mean psychosis symptom dimension scores for first episode psychosis patients with a diagnosis of schizophrenia, manic psychosis and other psychoses at first presentation to psychiatric services. The continuous symptom dimension scores were derived using the 'predict' post-estimation command in Stata following a confirmatory factor analysis of the Wallwork/Fortgang five-factor model [26] of the items from the Positive and Negative Syndrome Scale [234]. The five dimensions capture positive, negative, disorganised/concrete, excited, and depressed symptom items at first presentation to psychiatric services.

*p<0.05, ** p<0.01, ***p<0.001

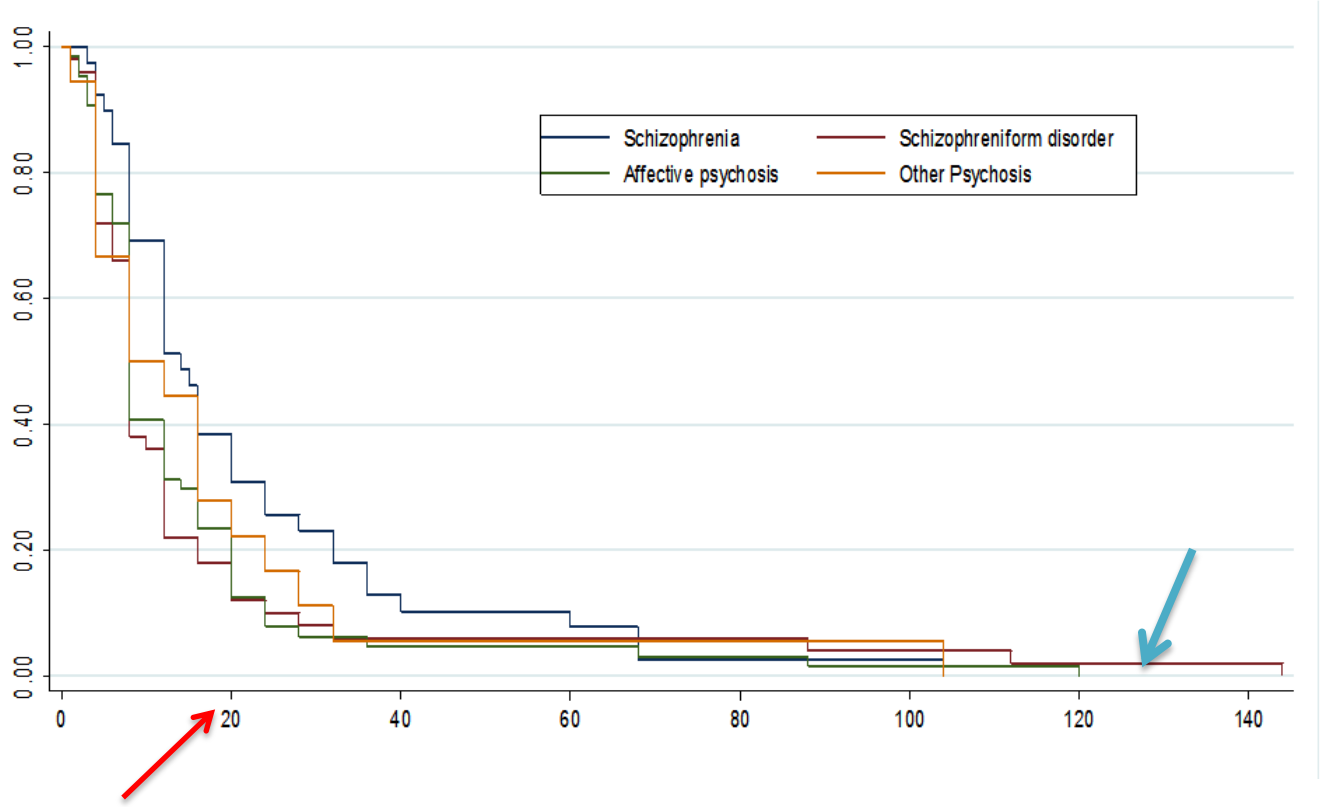
4.3.3. Time to remission

The rate of remission during the first four years of illness was 60.2% and the average time to the start of the first period of remission was 18.3 weeks (s.d.=26.0; median=8 weeks, IQR=5-20 weeks). Those who did not remit (*n*=74) showed more severe symptoms on the disorganised/concrete (*t*=1.99, df=184, *p*=0.05) symptom dimension compared to remitters at the time of study entry. Otherwise, remitters and non-remitters did not differ in severity of other symptom dimensions at baseline. Among *n*=112 patients who met criteria for remission, 18% were continually asymptomatic till the end of follow-up period. For these patients, the mean of time to remission was 19 weeks (median=5, IQR=4-20). Moreover, 26% of all remitters remitted within one month, 13% remitted within 12 weeks and 6.5% remitted between 68-144 weeks after first contact with mental health services.

4.3.4. Associations between time to remission and symptom dimensions vs diagnostic categories

Kaplan–Meier (K-M) survival curves of time to the first remission stratified by diagnostic categories are shown in **Figure 7**. This K-M survival curve illustrates that the average time to first remission was within 20 weeks; this is highlighted by the **RED** arrow in the figure 7. However, those patients who received a diagnosis of schizophreniform disorder at baseline took the longest time to achieve first remission after the first contact with mental health services; this is highlighted by the **BLUE** arrow in the Figure 7.

Figure 7. *Kaplan–Meier survival curve of the time from the first presentation to psychiatric services for psychosis to the start of the first period of remission, by traditional diagnostic categories*



The y axis illustrate the proportion of FEP out of the total=1 achieving the first remission after first contact with mental health services; the axes indicates when in *weeks*. For the purposes of this study the baseline diagnoses were grouped using DSM-IV codes into schizophrenia (295), schizophreniform disorder (295.40), and affective psychoses (296, 296.24, 296.44). Because the diagnosis of schizoaffective disorder does not have a clear construct, as it is a mixture of schizophrenia and affective symptoms,[252] and a relatively small sample of patients had this diagnosis, I combined schizoaffective disorder with the other psychoses in the analyses and labelled this group as 'other psychoses' (295.70, 297.1, 298.9).

Multivariate accelerated failure time (AFT) model estimates of time to first remission are provided in **Table 10.** Over the first four years of follow-up, the positive symptom dimension measured at baseline was associated with an average of 14.6 weeks (β=0.07, 95% CI=0.01-0.13), the excited dimension with an average of 35.4 weeks (β=0.17, 95% CI=0.03-0.41) and the disorganised/concrete dimension with an average of 20.8 weeks (β=0.10, 95% CI= 0.01-0.19) longer to first remission after first contact with psychiatric services. The combination of all five symptom dimensions led to a significant association with the time to first remission with an average increase of 8.3 weeks to remission (β=0.04, 95% CI=0.01-0.07). The baseline diagnosis of schizophrenia was significantly associated with an average of 52 weeks longer to first remission compared to non-schizophrenia diagnoses (β=0.25, 95% CI=0.06-0.43). The combination of the baseline diagnosis of schizophrenia with all five symptom dimensions was associated with 10.4 weeks longer to remission (β=0.05, 95% CI=0.02-0.07).

Table 10. *Multivariate Accelerated Failure Time model estimating difference in time to the start of first remission after first contact with mental health services for psychosis*

Clinical characteristics at first contact	β (SE)	95% CI
Symptom dimensions		
Positive	0.07 (0.03)**	0.01-0.13
Excited	0.17 (0.07)**	0.03-0.31
Negative	0.03 (0.04)	-0.06-0.11
Disorganised/Concrete	0.10 (0.05)**	0.01-0.19
Depressed	-0.02 (0.08)	-0.17-0.13
All 5 psychosis dimensions	0.04 (0.02)***	0.01-0.07
Diagnostic categories		
Schizophrenia	0.25 (0.09)***	0.06-0.43
Schizophreniform disorder	-0.18 (0.10)	-0.37-0.01
Affective Psychoses	-0.05 (0.08)	-0.21-0.12
Other Psychoses	-0.03 (0.10)	-0.22-0.16
All four diagnostic categories	-0.03 (0.02)	-0.08-0.02
Combination of both approaches		
Schizophrenia diagnosis and all 5 psychosis dimensions	0.05 (0.01)***	0.02-0.07

Effect size is indicated by β coefficient and standard error (SE) from the accelerated failure time survival model. CI, confidence interval. All analyses adjusted for age at the time of first contact with mental health services for psychosis, duration of untreated psychosis and substance use measured during the four-year follow-up period and antipsychotic medication adherence over the course of follow-up.

*p<0.05, ** p<0.01, ***p<0.001

4.3.5. Selecting the best model for predicting time to remission

The results of the BIC and $_{\Delta}$BIC analyses are presented in **Table 11**. Compared to all four categorical diagnoses (Models 7-10, BIC range from 160.71 to 167.45), using symptom dimensions individually as predictors of time to remission did not lead to models with better predictive powers (Models 1-5, BIC range from 165.48 to 171.30). Using all four categorical diagnoses in combination produced a model (Model 11, BIC=165.83) with an equal predictive power to the model that combined all five symptom dimensions (Model 6, BIC=163.61) in predicting time to first remission. Further analyses showed that supplementing the baseline schizophrenia diagnosis with five symptom dimensions generated the best model fit (Model 12, BIC=154.50) for predicting time to first remission. The $_{\Delta}$BIC analyses highlighted that none of the five symptom dimensions ($_{\Delta}$BIC range from 10.98 to 16.80), nor the diagnostic categories ($_{\Delta}$BIC range from 6.21 to 12.95), produced a robust model fit compared to Model 12.

Table 11. *Comparisons of the fit of all significant models using BIC scores and $_{\Delta}$BIC*

Models	Predictors of time to first remission	BIC	$_{\Delta}$BIC
Symptom dimensions			
Model 1	Positive dimension	165.48	10.98
Model 2	Excited dimension	165.54	11.04
Model 3	Negative	170.96	16.46
Model 4	Disorganised/Concrete	166.45	11.95
Model 5	Depressed	171.30	16.80
Model 6	All 5 psychosis dimensions	163.61	9.11
Diagnostic categories			
Model 7	Schizophrenia	160.71	6.21
Model 8	Schizophreniform disorder	162.52	8.02
Model 9	Affective Psychoses	167.20	12.70
Model 10	Other Psychoses	167.45	12.95
Model 11	All four diagnostic categories	165.83	11.33
Combination of both approaches			
Model 12	**Schizophrenia diagnosis and all 5 psychosis dimensions**	**154.50**	**0**

BIC, Bayesian Information Criterion; $_{\Delta}$BIC is defined as the model minus the model with the lowest BIC score

All models adjusted for age at the time of first contact with mental health services for psychosis, duration of untreated psychosis and substance use measured during the four-year follow-up period and antipsychotic medication adherence over the course of follow-up.

The model in bold provided the best fit (i.e., the lowest BIC score)

4.4. Discussion

In the present study 60% of 191 patients with FEP achieved remission during the first four years after first contact with mental health services for psychosis; 18% of this group were continually asymptomatic till the end of follow-up period. A quarter of all remitters had remitted within one month and a minority (7%) took up to 33 months to achieve remission; however, the majority of the patients remitted within 4 months after first contact with mental health services. I found that the positive, excited and disorganised/concrete dimensions of psychosis were important predictors of time to first remission in this sample.

4.4.1. Time to remission and symptom dimensions vs diagnostic categories

Although a previous study showed that negative symptoms of psychosis measured by PANSS at baseline differentiated non-remitters from remitters at the end of a 16-year course of illness [256], I did not find evidence to suggest that the negative symptom dimension had an impact on time to first remission during the 4-year of follow-up in my sample. This may have been due to the shorter time-frame of my study. It is also possible that people with predominantly negative symptoms may be less likely to be treated as inpatients and thus may have been under-represented in my sample which recruited a large proportion of patients from psychiatric wards.

My results highlight that the positive, excited and disorganised/concrete dimensions of psychosis are important predictors of longer time to first remission. The psychosis symptoms that constituted these three dimensions in my study all expressed at onset have been shown to correlate with a poor therapeutic response to antipsychotic medications [257]. It therefore could be speculated that patients in the present study with these symptom dimensions at presentation may take longer to respond to treatments with antipsychotic medications, potentially delaying attainment of remission. Demonstrating that specific symptom dimensions are predictive of time to remission in FEP is an important first step in mapping these putative markers of response onto illness outcome. My results also showed that a diagnosis of schizophrenia was associated with a longer time to first remission. This observation is consistent with a characterisation of this disorder as one with lower rates of remission and a more disabling course than other psychotic disorders [258, 259].

In contrast to my hypothesis, the psychosis symptom dimensions were not superior to the traditional diagnostic categories in predicting time to first remission. In fact, I found that the combination of the diagnosis of schizophrenia with all five symptom dimensions produced the best model in predicting a longer time to remission. As there are no specific markers to guide the choice of treatment and to stratify patients with FEP by treatment response [260], I provide novel findings that may serve as important prognostic markers indicative of those subgroups who will take substantially longer to respond to treatment (as indicated by remission status) within the first four years after first contact with psychiatric services.

4.4.2. Methodological considerations

The five factor model of psychosis symptoms employed in the present study was selected for being a consensus model derived from existing studies [26] that has been shown to be optimal for use in FEP samples [27]. Similarly, I employed the operationalised definition of remission and time to remission that has previously been utilised in an earlier study conducted in an overlapping geographical region [74, 240] ensuring comparability of the results between the studies. The symptom dimensions were founded on the PANSS which has previously been shown to be resilient to the effects of age, severity of symptoms, chronicity of illness [261] and short-term medication withdrawal [262].

The findings of the present study should be interpreted in light of methodological limitations. It is important to note that nearly 80% of the patients were recruited to the original GAP study from inpatient units; this may imply that very early remitters may not have been fully represented from the start. Due to relatively small sample size, I was unable to explore associations between the depressive psychotic disorders and time to remission. Finally, many diagnostic categories assigned to patients on first contact with mental health services may either be provisional or likely to change over the illness course [263], as seen in my sample with a relatively high number of patients with a diagnosis of schizophreniform disorder. Nevertheless, in the present study I focused on the baseline diagnosis, rather than the diagnosis obtained at the end of the follow-up period, to emulate the naturalistic setting for all patients with FEP when predicting time to remission depending on the diagnosis received on the very first contact with the psychiatric services.

4.5. Summary and concluding remarks

There has been much recent debate concerning the relative clinical utility of symptom dimensions versus conventional diagnostic categories in psychosis patients. In this study I investigated whether symptom dimensions at presentation for FEP better predicted time to remission than diagnostic categories over a four-year follow-up. My sample comprised 191 FEP patients aged 18-65 years presenting for the first time to psychiatric services in South London, UK. Psychopathology was assessed at baseline with the Positive and Negative Syndrome Scale and five symptom dimensions were derived using Wallwork/Fortgang's model; baseline diagnoses were grouped using DSM-IV codes. Time to start of first remission was ascertained from clinical records. The Bayesian Information Criterion (BIC) was used to find the best fitting accelerated failure time model of dimensions, diagnoses and time to remission. My results showed that 60% of patients remitted over the four years since first presentation to psychiatric services, and the average time to start of first remission was 18.3 weeks (s.d.=26.0). The positive, excited and disorganised/concrete symptom dimensions as well as baseline categorical diagnosis of schizophrenia predicted time to remission. However, a combination of the DSM-IV diagnosis of schizophrenia with all five symptom dimensions led to the best model for predicting a longer time to first remission. These results indicate that the use of a combination of five symptom dimensions and the traditional diagnostic category of schizophrenia provides a more robust prediction of the length of time that it would take for patients to respond to treatment after the first contact with mental health services for FEP.

CHAPTER 5 STUDY 3

Patterns of illness and care over the 5 years following onset of psychosis in Black African, Black Caribbean and White British patients

5.1. Introduction

Psychiatric epidemiology has consistently demonstrated that the incidence rates of psychotic disorders are considerably elevated among those of Black ethnicity residing in the UK compared to the host population[59-61]. The evidence further suggests that individuals of Black ethnicity are more likely to make contact with mental health services via admissions under Mental Health Act (MHA) legislation[62] , in many cases with police present on an admission [69, 194], or admission to high-security psychiatric hospitals [195] compared to White British patients. These findings were echoed in the ÆSOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study, which was one of the first studies of people with first onset psychosis (FEP) in England [61]. There are some indications that this pattern of more compulsory care persists over the course of their illness [185, 196, 199].

Over the past 20 years there has been an increased focus on specialist early intervention services for first episode psychosis (FEP) [264, 265] which ignited recognition that individuals with psychotic disorders still can experience symptomatic improvements and regain a degree of social and occupational functioning [266]. The evidence is consistent that one-third of patients with psychosis recover [74, 267]. Yet, it is still unclear whether this figure applies to Black ethnic groups. Reports are mixed in relation to the symptomatic remission in Black populations with some reporting that remission is more common in Black ethnic groups [198], while others argue an opposite view [199]. Importantly, earlier research into longitudinal illness trajectory across ethnic groups is marked by methodological limitations, such as small sample sizes [196], and a tendency to neglect the diversity in culture, religious beliefs and life experience between Black African and Black Caribbean populations by combining these ethnic groups in analyses [185, 196-198]. Furthermore, some investigators have limited their sample to those with diagnosis of schizophrenia only [69, 197]; or who had been re-admitted during a follow up period, and as such bias results towards poorer outcomes [49].

Cumulatively, previous research has not provided us with a comprehensive picture of the true course of psychotic disorders in Black African and Black Caribbean ethnic groups, and whether the intensity of care delivered to Black ethnic groups reflects the severity of their psychopathology. Therefore, using a quasi-prospective cohort design and utilising the data from a large and well-characterised sample of patients with FEP, I sought to investigate clinical and social outcomes in Black African and Black Caribbean ethnic groups compared with White British patients. I further tested whether the intensity of care delivered to Black ethnic groups was reflected in their overall functional disability and illness severity in the due illness course after first contact with mental health services for psychosis. My null hypothesis was that the clinical course and pattern of care in patients of Black ethnicity would not be different from patients of White British ethnicity.

5.2. Methods

Detailed description of the methods behind the baseline assessment and follow up as well as for tracing the patients over the first five years of illness after he first contact with mental health services are provided in Sections 2.3-2.3.6.3., pages 69-77

5.2.2. Statistical analysis

5.2.1. Statistical Analyses

I described primary outcomes using frequencies, percentages, mean and standard deviations, median and interquartile ranges (IQR). Between groups comparisons were made using x^2 tests for categorical variables; ANOVA tests, or Kruskal-Wallis tests, for continuous variables; rank x^2 tests for count data. All analyses were two-tailed, and a P-value≤0.05 was considered statistically significant. All analyses were conducted in STATA release 14 (STATA Corp LP, USA).

5.3. Results

5.3.1. Sample at baseline

The baseline sample in this study comprised 297 FEP patients. Of these, 111 (37.4%) were of White British, 110 (37.0%) were of Black African and 76 (25.6%) were of Black Caribbean ethnicity. At the time of first contact with mental health for psychosis, a higher proportion of Black Caribbean patients lived alone (x^2=6.98, df=2, p=0.03) and were unemployed (x^2=7.24, df=2, p=0.03) compared to White British and Black African ethnic groups. There were no other differences between the ethnic groups at the time of first contact with mental health services for psychosis (Table 12)

Table 12. *Baseline diagnosis, socio-demographic and clinical characteristics, by ethnicity*

Baseline socio-demographic and clinical characteristics	Total *n*=297	White British *n*=111 (37.4)	Black African *n*=110 (37.0)	Black Caribbean *n*=76 (25.6)	Statistics	df	*p*-value
Age $_{years}$, Mean (s.d.)	28.3 (8.8)	29.5 (9.9)	26.8 (7.5)	28.6 (8.6)	F=2.51	284	0.08
DUP $_{days}$, Mean (s.d.)	39.2 (126.3)	41.6 (148.4)	36.8 (103.7)	40.2 (131.8)	F=0.02[a]	173	0.98
Gender, *n* (%)							
Women	100 (34.6)	34 (31.5)	34 (31.8)	32 (43.2)	chi^2=3.28	2	0.19
Men	189 (65.4)	74 (68.5)	73 (68.2)	42 (56.8)			
Diagnosis, *n* (%)							
Non-affective psychosis	185 (75.2)	63 (71.6)	71 (75.5)	51 (79.7)	chi^2=1.31	2	0.52
Affective psychosis	61 (24.8)	25 (28.4)	23 (24.5)	13 (20.3)			
Living arrangements, *n* (%)							
Alone	69 (39.4)	26 (37.1)	23 (32.4)	20 (58.8)	chi^2=6.98	2	0.03
With partner or parents	106 (60.6)	44 (62.9)	48 (67.6)	14 (41.2)			
Relationship status, *n* (%)							
Single	130 (74.3)	52 (74.3)	52 (73.2)	26 (76.5)	chi^2=0.13	2	0.94
Stable relationship	45 (25.7)	18 (25.7)	19 (26.8)	8 (23.5)			
Employment, *n* (%)							
Unemployed	114 (66.3)	46 (68.7)	40 (56.3)	28 (82.4)	chi^2=7.24	2	0.03
Employed	58 (33.7)	21 (31.3)	31 (43.7)	6 (17.6)			
GAF symptoms, Mean (s.d.)	46.7 (20.1)	47.1 (21.0)	47.6 (18.9)	43.6 (21.2)	F=0.31	119	0.73
GAF disability, Mean (s.d.)	55.1 (18.3)	56.1 (19.9)	57.0 (16.2)	48.1 (18.2)	F=1.91	119	0.15

s.d., standard deviations; DUP, duration of untreated psychosis; d.f., degrees of freedom; GAF, global assessment of functioning

[a] the results are presented after log-transformation

A flow chart depicting how the cases were traced and administrative outcomes is presented in **Figure 8**. Approximately 5 years ($mean_{years}$=5.1, s.d.=2.4; 1,251 person years) after first contact with mental health services, a total of 11 (3.7%) patients had died; but information on longitudinal outcomes was available for 7 of these, thus these 7 patients were included in all analyses. Twelve (4.1%) patients had migrated, and 6 (2.1%) patients moved out from the catchment area. Additional 7 (2.4%) patients were excluded as I did not have information on follow up and their details were not available at baseline to enable me to trace them via ONS/GRO tracing procedures. I was unable to trace the whereabouts for 23 (7.9%) patients. Those patients who had died during the follow up period without any information on the course of their illness (*n*=4 (1.4%)) were older ($mean_{years}$=44.5, sd=18.4) (F=4.05, df=282, *p*=0.003); and those who emigrated tended to be of Black African ethnicity (x^2=18.36, df=8, *p*=0.02) (Table 13). Cumulatively, I successfully traced 92.1% of my original sample and the full information at follow up was available for 84.5% (*n*=245/290) patients. FEP patients who were lost to follow-up were not significantly different in the baseline characteristics from patients who had full follow up data (Table 14).

Figure 8. *Flow chart documenting how patients were traced and administrative outcomes five years after first contact with mental health services for first episode psychosis*

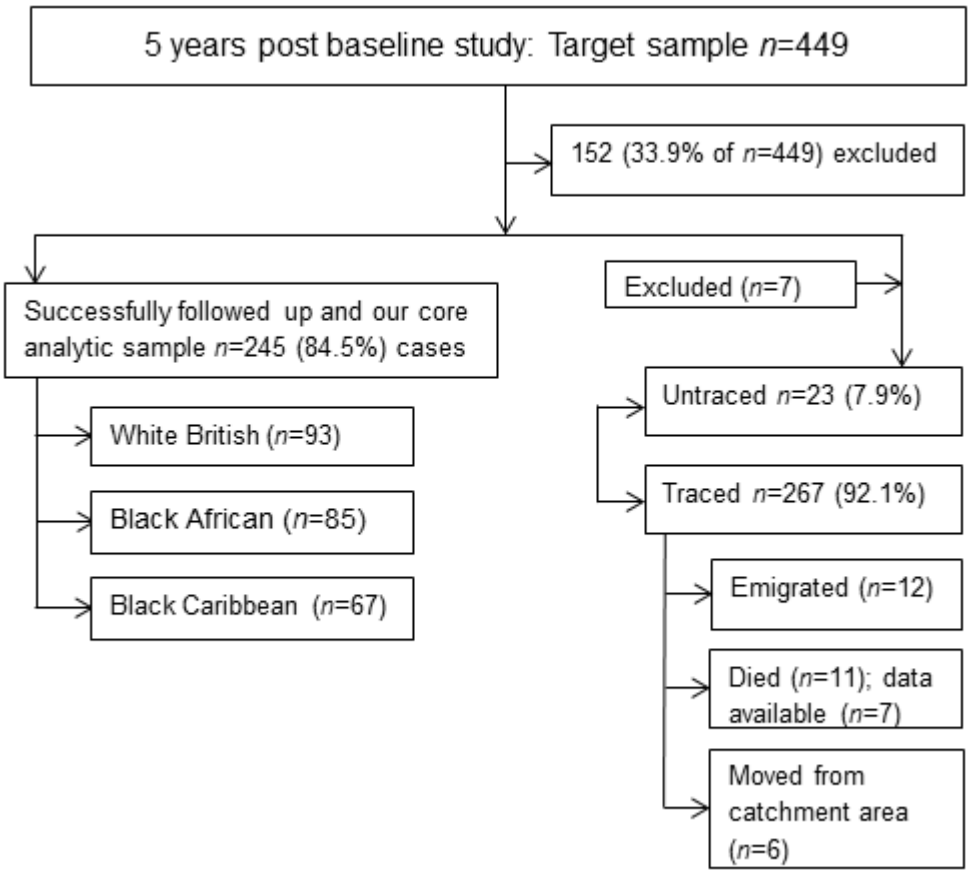


Table 13. *Baseline demographic characteristics by administrative outcome*

Baseline demographic characteristics	Followed up *n*=245 (84.5%)	Unable to trace *n*=23 (7.9%)	Abroad *n*=12 (4.1%)	Died *n*=4 (1.4%)	Moved *n*=6 (2.1%)	Statistics	df	*p*-value
Gender, *n* (%)								
Female	82 (34.2)	7 (30.4)	7 (58.3)	2 (50.0)	1 (16.7)	Ch^2=4.44	4	0.35
Male	158 (65.8)	16 (69.6)	5 (41.7)	2 (50.0)	5 (83.3)			
Age at first contact, *n* (%)	27.9 (8.1)	29.1 (11.7)	26.3 (5.9)	44.5 (18.9)	29.8 (4.7)	F=4.05	282	0.003
Ethnicity, *n* (%)								
White British	93 (38.0)	9 (39.1)	1 (8.3)	2 (50.0)	3 (50.0)	Chi^2=18.36	8	0.02
Black African	84 (34.7)	10 (43.5)	11 (91.7)	1 (25.0)	1 (16.7)			
Black Caribbean	67 (27.3)	4 (17.4)	-	1 (25.0)	2 (33.3)			
Living arrangements, *n* (%)								
Alone	61 (41.5)	2 (15.4)	3 (37.5)	1 (33.3)	2 (50.0)	Chi^2=3.66	4	0.45
With partner or parents	86 (58.5)	11 (84.6)	5 (62.5)	2 (66.7)	2 (50.0)			
Relationship status, *n* (%)								
Single	107 (72.8)	9 (69.2)	8 (100.0)	2 (66.7)	4 (100.0)	Chi^2=4.59	4	0.33
Stable relationship	40 (27.2)	4 (30.8)	-	1 (33.3)	-			

s.d., standard deviations; d.f., degrees of freedom

Table 14. *Baseline demographic characteristics for those who were lost to follow up compared to individuals with full follow up data*

Baseline sample characteristics	Lost to follow up *n*=45 (15.5%)	Followed up *n*=245 (84.5%)	Statistics	df	*p*-value
Age $_{years}$, Mean (s.d.)	30.1 (11.5)	27.9 (8.1)	t=-1.46	281	0.15
Gender, *n* (%)					
Women	17 (37.8)	82 (34.2)	chi^2=0.22	1	0.64
Men	28 (62.2)	158 (65.8)			
Ethnicity, *n* (%)					
White British	15 (33.3)	93 (38.0)	chi^2=5.04	2	0.08
Black African	23 (51.1)	85 (34.7)			
Black Caribbean	7 (15.6)	67 (27.3)			
Living arrangements, *n* (%)					
Alone	8 (28.6)	61 (41.5)	chi^2=1.65	1	0.20
With partner or parents	20 (71.4)	86 (58.5)			
Relationship status, *n* (%)					
Single	23 (82.1)	107 (72.8)	chi^2=1.08	1	0.30
Stable relationship	5 (17.9)	40 (27.2)			
GAF symptoms, Mean (s.d.)	41.5 (17.0)	47.7 (20.6)	t=1.24	118	0.22
GAF disability, Mean (s.d.)	54.7 (18.4)	55.1 (18.4)	t=0.09	118	0.93

s.d., standard deviations; d.f., degrees of freedom; GAF, global assessment of functioning

5.3.2. Core analytic sample

My core analytic sample comprised 245 (82.5% of *n*=297) FEP patients with an average follow-up length of 5 years after first contact with mental health services for psychosis. This sample encompassed 93 (38.0%) patients of White British, 85 (34.7%) patients of Black African and 67 (27.3%) patients of Black Caribbean ethnicity. Patients of Black Caribbean ethnicity had the longest length of follow up ($mean_{years}$=5.6, sd=2.6) compared to White British ($mean_{years}$=4.9, sd=2.4) and Black African ($mean_{years}$=4.9, sd=2.2) ethnic groups; though this difference did not meet the standard level for statistical significance (F=2.12, df=243, *p*=0.12). Sixty six percent (158/240 cases) of the total sample were of male gender with Black African patients being particularly likely to be male (x^2=5.39, df=2, *p*=0.07) (Table 15).

Table 15. *Demographic characteristics by ethnicity at 5 years follow up*

Demographic characteristics	Total *n*=245	White British *n*=93 (38.0%)	Black African *n*=85 (34.7%)	Black Caribbean *n*=67 (27.3%)	Test statistics	df	*p*-value
Follow up, Mean (s.d.)	5.1 (2.4)	4.9 (2.4)	4.9 (2.2)	5.6 (2.6)	F=2.12	243	0.12
Gender, *n* (%)							
Women	82 (34.2)	29 (31.5)	23 (28.1)	30 (45.5)	x^2=5.39	2	0.07
Men	158 (65.8)	63 (68.5)	59 (71.9)	36 (54.5)			

s.d., standard deviation; d.f., degrees of freedom

5.3.3. Clinical presentation over the follow up period

Clinical illness course for the entire follow up period after first contact with mental health services for psychosis by ethnicity is presented in **Table 16**. Over the 5-year follow up period, 63.1% (*n*=149/236) of the overall sample reported remission and 28.4% (*n*=63/222) met criteria for recovery at least once, with a median duration of the baseline episode of 8 weeks (IQR=6-20). White British, Black African and Black Caribbean ethnic groups did not differ in these outcomes. During the follow up period, no ethnic group showed a more rapid deterioration in overall illness severity and functional disability.

Table 16. *Clinical outcomes over the first five years after first contact with mental health services for psychosis, by ethnicity*

Clinical outcomes	Total *n*=245	White British *n*=93 (38.0%)	Black African *n*=85 (34.7%)	Black Caribbean *n*=67 (27.3%)	Test statistics	df	*p*-value
Duration of baseline episode, w Median (IQR)	8 (6-20)	8 (4-20)	8 (4-16)	8 (8-20)	2.77[a]	2	0.25
Symptomatic remission, ever *n* (%)	149 (63.1)	53 (60.9)	55 (64.7)	41 (64.1)	0.30[b]	2	0.86
Symptomatic recovered, ever *n* (%)	63 (28.4)	25 (31.3)	21 (25.3)	17 (28.8)	0.64[b]	2	0.73
GAF symptoms change Mean (sd)	13.3 (26.8)	14.9 (27.1)	12.1 (25.1)	11.8 (30.6)	0.14[c]	95	0.87
GAF disability change Mean (sd)	9.4 (23.9)	8.6 (25.6)	6.7 (21.9)	16.8 (23.6)	1.12[c]	96	0.33

w, weeks; sd, standard deviation; df, degrees of freedom, GAF, global assessment of functioning

[a] rank test x^2 for the count data

[b] x^2 tests for categorical variables

[c] ANOVA test for continuous variables

5.3.4. Pattern of care over the follow up period

Patterns of care during the follow up period after first contact with mental health services for psychosis by ethnicity are presented in **Table 17**. Excluding admissions on first contact with mental health services, 70% of my sample was re-admitted at least once, and 30% of the sample had ≥3 hospital re-admission during the follow up period. Patients of Black Caribbean ethnicity had a shorter time to first re-admission after first contact ($median_{weeks}$=46.2, IQR=23.6-114.0) compared with Black African and White British ethnic groups (rank test x^2=5.32, df=2, p=0.07). Black Caribbean ethnic group had the longest ($median_{days}$=141.0, IQR=42.0-362.0) and patients of White British ethnicity had the shortest ($median_{days}$=69.0, IQR=38.0-173.0) overall length of time spent in psychiatric units; however, neither of these differences met the standard threshold for statistical significance. Further, a higher proportion of Black African and Black Caribbean ethnicity had compulsory re-admissions (x^2=17.34, p=0.002) and instances of police involvement during an admission to a psychiatric unit (x^2=22.82, p<0.001) compared with White British ethnic group.

Table 17. *Service utilisation over the first five years after first contact with mental health services for psychosis, by ethnicity*

Service utilisation	Total *n*=245	White British *n*=93 (38.0%)	Black African *n*=85 (34.7%)	Black Caribbean *n*=67 (27.3%)	Test statistics	df	*p*-value
Time to first readmission, w							
Median (IQR)	50.1 (15.1-107.6)	51.4 (13.3-111.4)	52.1 (16.1-93.6)	46.2 (23.6-114.0)	5.32[a]	2	0.07
Admissions, *n* (%)							
None	71 (30.7)	30 (35.7)	21 (25.3)	20 (31.3)	4.89[b]	4	0.30
1-2	93 (40.3)	33 (39.3)	39 (47.0)	21 (32.8)			
>3	67 (29.0)	21 (25.0)	23 (27.7)	23 (35.9)			
Length of inpatient stay, d							
Median (IQR)	107.0 (38.5-275.5)	69.0 (38.0-173.0)	122.5 (37.0-300.0)	141.0 (42.0-362.2)	4.93[a]	2	0.09
Compulsory, *n* (%)							
None	60 (34.3)	29 (46.8)	12 (19.1)	19 (38.0)	17.34[b]	4	0.002
1-2	80 (45.7)	26 (41.9)	38 (60.3)	16 (32.0)			
>3	35 (20.0)	7 (11.3)	13 (20.6)	15 (30.0)			
Police involved, *n* (%)							
None	74 (42.5)	35 (56.5)	14 (22.6)	25 (50.0)	22.82[b]	4	<0.001
1-2	79 (45.4)	24 (38.7)	40 (64.5)	15 (30.0)			
>3	21 (12.1)	3 (4.8)	8 (12.9)	10 (20.0)			
Community services							
Median (IQR)	3 (2-5)	3 (2-4)	3 (2-5)	3 (2-5.5)	3.19[a]	2	0.20

w, weeks, d, days, IQR, inter-quartile range; sd, standard deviation; df, degrees of freedom

[a] rank test x^2 for the count data

[b] x^2 tests for categorical variables

5.3.4.1. Does ethnicity predict the pattern of treatment provided over the first five years of illness?

Longitudinal service use outcomes in Black African and Black Caribbean ethnic groups compared to White British ethnicity independent of confounding factors such as age at first contact with mental health services, gender, and baseline diagnoses are presented in **Table 18**. During the 5-year follow up, patients of Black African ethnicity were at a greater risk to be re-admitted at least once (HR=1.57, 95% CI=1.06-2.36), to be admitted under MHA (HR=2.07, 95% CI=1.28-3.33) or have police involved prior to or during a re-admission (HR=2.49, 95% CI=1.47-4.19) compared to their White British counterparts. Further, patients of Black African ethnicity were at a greater risk for multiple compulsory re-admissions (IRR=1.73, 95% C=1.17-2.56) and police involvement during re-admissions (IRR=2.17, 95% CI 1.32-3.56) over the follow up period than patients of White British ethnicity. Both Black African (IRR=1.48, 95% CI=1.06-2.10) and Black Caribbean (IRR=1.48, 95% CI=1.03-2.11) ethnic groups were at a greater risk to have a high number of re-admission than their White British counterparts.

Table 18. *Longitudinal service use outcomes in Black African and Black Caribbean ethnic groups compared to White British ethnicity independent of confounding factors such as age at first contact with mental health services, gender, and baseline diagnoses*

Service utilisation	White British *n*=93 (38.0%)	Black African *n*=85 (34.7%)	Black Caribbean *n*=67 (27.3%)
Re-admitted, ever			
HR (95% CI)	-	1.57** (1.06-2.34)	1.06 (0.69-1.63)
Admissions, number			
IRR (95% CI)	-	1.48** (1.06-2.10)	1.48 ** (1.03-2.11)
Length of inpatient stay			
IRR (95% CI)	-	1.72 (0.87-3.42)	1.24 (0.59-2.60)
Compulsory, number			
IRR (95% CI)	-	1.73*** (1.17-2.56)	1.44 (0.95-2.19)
Compulsory, ever			
HR (95% CI)	-	2.07*** (1.28-3.33)	1.17 (069-1.99)
Police involved, number			
IRR (95% CI)	-	2.17*** (1.32-3.56)	1.61 (0.95-2.74)
Police involvement, ever			
HR (95% CI)	-	2.49*** (1.47-4.19)	1.28 (0.71-2.31)
Regular community services, number			
IRR (95% CI)	-	1.25** (1.04-1.51)	1.17 (0.96-1.43)
Intensive community services, number			
IRR (95% CI)	-	1.23 (0.95-1.59)	1.08 (0.83-1.42)

IRR, incidence rate ratio; CI, confidence intervals; HR, hazard ration;
Adjusted for age at first contact with mental health services, gender and baseline diagnosis
*p<0.05, ** p<0.01, *** p<0.001

Next I adjusted the models which produced significant results in the above set of analyses for additional variables: living arrangements, relationship status and substance use over the follow up period. The aim of these analyses was to investigate whether the significant results were explained by these factors (**Table 19**). The risk for Black Africa patients being re-admitted at least once (HR=1.77, 95% CI=1.25-2.72), to be admitted under MHA (HR=2.17, 95% CI=1.29-3.63) or have police involved prior to or during a re-admission (HR=2.75, 95% CI=1.56-4.86), though slightly attenuated, remained significant, compared to their White British counterparts. Similarly, patients of Black African ethnicity were still at a greater risk for multiple compulsory re-admissions (IRR=1.64, 95% CI=1.07-2.51) and even more so for police being involved during re-admissions (IRR=2.42, 95% CI=1.41-4.13) over the follow up period than patients of White British ethnicity. The risk for a higher number of re-hospitalisations to the psychiatric wards in patients of Black African and Black Caribbean ethnicity remained significant after adjusted analysis for living arrangements, relationship status and substance use over the follow up period; though it was considerably reduced for Black Caribbean ethnic group.

Table 19. *Longitudinal service use outcomes in Black African and Black Caribbean ethnic groups compared to White British ethnicity independent of confounding factors such as age at first contact with mental health services, gender, and baseline diagnoses and follow up variables (i.e., living arrangements, relationship status and substance use over the follow up period)*

Service utilisation	White British *n*=93 (38.0%)	Black African *n*=85 (34.7%)	Black Caribbean *n*=67 (27.3%)
Re-admitted, ever			
HR (95% CI)	-	1.77** (1.25-2.72)	1.13 (0.70-1.81)
Admissions, number			
IRR (95% CI)	-	1.58** (1.08-2.33)	1.49* (1.00-2.24)
Compulsory, number			
IRR (95% CI)	-	1.64** (1.07-2.51)	1.42 (0.90-2.23)
Compulsory, ever			
HR (95% CI)	-	2.17*** (1.29-3.63)	1.19 (0.66-2.13)
Police involved, number			
IRR (95% CI)	-	2.42*** (1.41-4.13)	1.77 (0.99-3.14)
Police involvement, ever			
HR (95% CI)	-	2.75 *** (1.56-4.86)	1.39 (0.73-2.64)
Regular community services, number			
IRR (95% CI)	-	1.30 (0.98-1.72)	1.05 (0.77-1.41)

IRR, incidence rate ratio; CI, confidence intervals; HR, hazard ration;
Adjusted for age at first contact with mental health services, gender, living arrangement, substance use during and relationship status during the follow up period and the duration of the follow up period
*p<0.05, ** p<0.01, *** p<0.001

5.3.5. Socio-demographic characteristics over the follow up period

By the end of the follow up period, a higher proportion of Black Caribbean patients lived alone (61.2% of *n*=67); while a substantial proportion of Black African ethnic group (25.3% of *n*=93) lived in a supported accommodation (x^2=10.88, df=2, *p*=0.03) as shown in **Table 20**. A lower proportion of White British patients were single (67% of *n*=91) compared to Black African (83.3% of *n*=84) and Black Caribbean (81.8% of *n*=66) ethnic groups (x^2=7.81, df=2, *p*=0.02). Moreover, 26% (*n*=17/66) of White British (compared to 8% (*n*=6/72) of Black African and 5% (*n*=3/56) of Black Caribbean ethnic groups) lived in privately rented accommodations; whereas, 93% (*n*=52/56) of Black Caribbean ethnic group were housed by local housing association services (x^2=25.05, df=4, *p*<0.001).

Table 20. *Socio-demographic characteristics by the follow up period, by ethnicity*

Demographics at follow up	Total *n*=245	White British *n*=93 (38.0%)	Black African *n*=85 (34.7%)	Black Caribbean *n*=67 (27.3%)	Test statistics	df	*p*-value
Living arrangement, *n* (%)							
Alone	116 (47.9)	39 (42.4)	36 (43.4)	41 (61.2)	10.88[a]	4	0.03
Not alone	80 (33.1)	39 (42.4)	26 (31.3)	15 (22.4)			
Supported accommodation	46 (19.0)	14 (15.2)	21 (25.3)	11 (16.4)			
Relationship status, *n* (%)							
Single	185 (76.8)	61 (67.0)	70 (83.3)	54 (81.8)	7.81[a]	2	0.02
Stable relationship	56 (23.2)	30 (33.0)	14 (16.7)	12 (18.2)			
Employment, *n* (%)							
Unemployed	191 (81.6)	73 (86.9)	65 (76.5)	53 (81.5)	3.07[a]	2	0.22
Employed	43 (18.4)	11 (13.1)	20 (23.5)	12 (18.5)			
Type of accommodation, *n* (%)							
Owned	11 (5.7)	5 (7.6)	6 (8.3)	-	25.05[a]	6	<0.001
Housing association/Local authority rented	142 (73.2)	38 (57.6)	52 (72.2)	52 (92.9)			
Privately rented	26 (13.4)	17 (25.8)	6 (8.3)	3 (5.4)			
Homeless	15 (7.7)	6 (9.1)	8 (11.1)	1 (1.8)			

df, degrees of freedom

[a] x^2 tests for categorical variables

5.4. Discussion

In this study I investigated the differences in the illness trajectories and pattern of care between White British, Black African and Black Caribbean ethnic groups during the 5-year of follow up period. My findings highlight that during the first five years of illness after first contact with mental health services, the longitudinal trajectory of psychosis in patients of Black ethnicity is characterised by longer inpatient stays, higher rates of compulsory admissions and increased instances of police involvement during or shortly before a re-admission to a psychiatric hospital compared with patients of White British ethnicity. This pattern of care in Black ethnic groups was not reflected in their overall functional disability and illness severity in the due illness course or likelihood to report either remission or recovery during the follow up period.

5.4.1. Longitudinal course and outcome of first episode psychosis

In contrast to a previous 18-yearlong study conducted in the overlapping geographical region as our study [185], I did not observe that patients of Black ethnicity had significantly elevated rate of hospital re-admissions over the 5-year period of follow up compared with White British patients. Consistently with this early work though[185], my results highlighted that both Black African and Black Caribbean ethic groups had a longer total inpatient stay than their White British counterparts. While it may be argued that a longer time spent at psychiatric hospitals over the illness course may be an indicator of a more severe illness course in patients of Black ethnicity, it is equally plausible that patients' living arrangements were important contributing factors to these findings[268]. Indeed, a higher proportion of patients of Black ethnicity lived alone, was single or was housed by local authorities compared with their White British counterparts. This may suggest that longer inpatient stays may have been due to a lack of suitable accommodations after hospital discharges. Further, some have raised a cause for concern that ethnic minority patients underutilise psychiatric community services after contact with mental health services [196], my results showed nonetheless that this was not the case for Black African and Black Caribbean ethnic groups when compared to White British counterparts during my follow up period.

Previously, it has been reported that people of Black ethnicity were more likely to be compulsorily detained compared with patients of White ethnicity during one year [269], and two years of follow up [196]. My results showed that this still remains the case during first 5-years of

illness after first contact with mental health services for psychosis. It has been suggested that the risk for compulsory detentions is amplified by a reluctance to seek help during a mental health crisis among those of Black ethnicity [269, 270]. The alleged unwillingness to utilise the available services at the time of mental health crisis has been linked to a variety of factors including distrust of psychiatric services [271], lack of insight into mental health difficulties [272] and language barriers [270]. Cumulatively my findings suggest that the factors which led to a higher rate of compulsory admissions among Black individuals in the past have not yet diminished. Further, the results highlighted that the patients of Black African ethnicity tended to have multiple instances of police involvements during hospital re-admissions. It has previously been shown that family members of those of Black ethnicity contact the police more frequently at times of clinical deterioration in their relative [63]; though I was unable to test if this was a factor in the increased rates of compulsory admissions in Black cases.

Additionally, I found that the proportion of unemployed increased in White British and Black African ethnic group by the end of the follow up period. While it is common for individuals with psychosis to struggle to develop or maintain stable relationships [273], there was an increased proportion of single individuals in the Black African and Black Caribbean ethnic group compared with White British group. Cumulatively these findings suggest that patients of Black ethnicity become increasingly socially excluded as their illness progresses.

5.4.2. Methodological considerations

Generally, longitudinal studies tend to suffer from systematic bias due to non-random loss of information during the follow up period. Nonetheless, in the present study considerable efforts have been made to minimise this potential bias by establishing the whereabouts, deaths and emigration status for impressive 92% of my sample. The quality and completeness of information reported in the clinical notes for each case inevitably varied, which in turn may have introduced bias. It is possible that clinicians might not have always recorded in the electronic clinical notes when symptoms were present and thus in some instances patients may have been classified inaccurately as remitted or recovered. Having said that, the rates of remission and recovery identified in this study are consistent with earlier studies which collected data either from face-to-face interviews only [123] or extracted it retrospectively [102]. It is also feasible that some of patients might have sought or purchased mental healthcare for a psychotic disorder elsewhere, or sought alternative means to

manage their symptoms, and thus would not have been registered in the SLaM electronic notes or included in the present study. Similarly, those patients who were reluctant to seek help would not be included in our sample; this in turn may reduce generalisability of my results. Further, I was unable to investigate whether the longitudinal outcomes differed depending on the generation of immigrants my ethnic groups belong to. Since the female patients tend to have a less severe illness course [49], the small population of women in in sample may have steered the results to more severe end of the illness course. Finally, although the compared ethnic groups were not matched by age and sex considerable effects have been made to ascertain a sample of patients who were representative of the general population in age, gender, ethnicity, educational qualifications, and employment status at the time of the study entry.

5.5. Summary and concluding remarks

Previous research has not provided us with a comprehensive picture of the longitudinal course of psychotic disorders in Black people living in Europe. I sought to investigate clinical outcomes and pattern of care in Black African and Black Caribbean groups compared with White British patients during the first five years after first contact with mental health services for psychosis. In the present study I utilised 245 FEP cases aged 18-65 who presented to psychiatric services in 2005-2010 in South London (UK). Using the electronic psychiatric clinical notes in the South London and Maudsley NHS Foundation Trust (SLaM), I extracted extensive information on three domains - clinical, social, and service use. My results showed that differences remain in patterns of care among those of Black African, Black Caribbean and White British patients resident in London during the first five years after first contact with mental health services for psychosis. The longitudinal trajectory of psychosis in patients of Black ethnicity is characterised by longer inpatient stays, higher rates of compulsory admissions and increased instances of police involvement during or shortly before a re-admission to a psychiatric hospital compared with patients of White British ethnicity. The observed pattern of care in Black ethnic groups was not reflected in their overall functional disability and illness severity in the due illness course or likelihood to report either remission or recovery during the follow up period. The prognosis is also still poor in terms of social functioning and isolation among Black ethnic groups during their illness. Further study is required to establish whether these differences reflect social or clinical differences between ethnic groups. Nonetheless, my findings reiterate a greater need for action in health systems and social policy to challenge and reduce these disparities.

CHAPTER 6 STUDY 4

Clinical predictors of treatment resistance in first episode schizophrenia

6.1. Introduction

Treatment resistant schizophrenia (TRS) is a major cause of disability and functional impairment; it affects up to 30% of patients diagnosed with SZ [191]. In the UK, it is recommended that clozapine, which is the only evidence-based effective medication for TRS, be offered to people with SZ whose illness has not responded to treatment despite the sequential use of adequate doses of at least two different antipsychotic medications [192]. Early identification of patients who require clozapine has the potential to improve clinical outcomes and minimise the social and functional disability that results from prolonged psychosis [207-209].

The aim of this study was to identify baseline clinical and demographic risk factors, which were predictive of treatment resistance (TR) defined at the end of the first five years of illness. To achieve this, I tested associations between TR status and a number of risk predictors, including type and severity of symptoms, gender, age, ethnicity, duration of untreated psychosis (DUP) and premorbid level of functioning. Further, in this study I aimed to look for differential clinical and social factors between those who showed “early-resistance” TR (E-TR) and those with “late- resistance” TR (L-TR). I aimed to assess the differences between patients in the E-TR group and those who were not treatment resistant (non-TR), and patients with L-TR and those who were non-TR. I additionally compared the TR patients treated with clozapine with those who met the criteria for the TR but had not commenced clozapine, in terms of their baseline sociodemographic and clinical characteristics.

6.2. Methods

6.2.1. Sample

For this study, only those FEP cases who met criteria for the following ICD-10 diagnoses: F20.0, F25.0, F28.0, F29.0, (for this study I refer to these patients as schizophrenia spectrum psychosis; no cases of schizotypal disorder were included in this group) [274] were included at baseline. Age at first contact was further categorised into four groups based on the results of interquartile analyses (18-20, 21-25, 26-30, and >31 years).

6.2.2. Association Analysis

Rigde regression, which is a form of Penalised logistic regression (PLR), was used to analyse the relationship between the predictors for TR status. In order to accommodate potential confounders when there may be relatively few observed outcome events, Rigde regression penalises large, imprecise coefficient estimates by shrinking them towards zero, thereby reducing the overall variability in the model, and minimises the emergence of excessively wide confidence intervals for odds ratios. Therefore, the Rigde regression may be considered a more robust approach to elucidating risk more accurately than logistic regression analysis in small to medium-sized data sets with few confounding factors[275].

To explore the moderating effects of gender and ethnicity in predicting the risk for TR, I examined whether there were significant interactions between these variables and the independent predictors used to predict TR status at follow up.

Confounding factors were identified through correlation analyses between the primary outcome (i.e. TR vs non-TR at five years) and a number of clinical and sociodemographic factors measured at baseline and during the follow up period. All variables with $p<0.05$ were included in the final model as confounding factors. Consequently, I adjusted the PLR analyses for the following variables: age at first contact for psychosis, and living arrangements, employment status and substance use during the follow up period.

6.3. Results

6.3.1. Sample characteristics

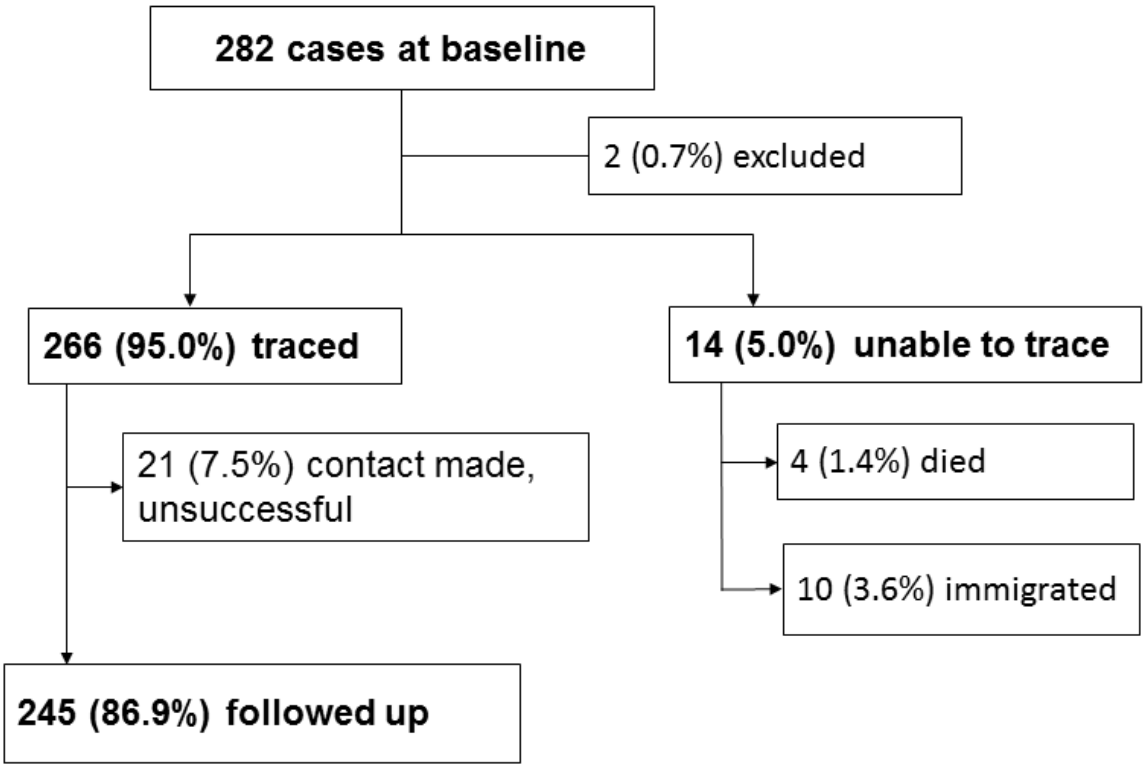
At baseline, the sample comprised *n*=282 cases with a diagnosis of a schizophrenia spectrum psychosis with the average age of 27.6 (sd=8.6) years. A flow chart depicting how the cases were traced and administrative outcomes is presented in **Figure 9**. Approximately 5 years ($mean_{year}$=5.4, SD=2.5; 1,310 persons years) after first contact for psychosis, *n*=10 (3.6%) emigrated, *n*=2 (0.7%) were excluded as these patient did not have information on follow up and their contact details were not available at baseline to enable to me trace them either via their GP or ONS/GRO tracing procedures, and *n*=4 (1.4%) had died. I was unable to trace a further *n*=21 (7.5%) cases. Those who died were significantly older than those who were followed up (**Table 21**).

Table 21. *Baseline demographic characteristics for those who were lost to follow up. These data are limited to first-episode schizophrenia spectrum patients and exclude cases of schizotypal disorder*

	Total	Followed up	Contact made, unsuccessful	Abroad	Died	Excluded	Statistics
n(%)	282	245 (86.9)	21 (7.5)	10 (3.6)	4 (1.4)	2 (0.7)	
Gender, *n*(%)							
Female		80 (32.6)	7 (33.3)	2 (20)	2 (50)	-	x^2=2.24 *df*=4 *p*=0.79
Male		165 (67.4)	14 (66.7)	8 (80)	2 (50)	2 (100)	
Age at first contact (mean (s.d.))	27.6 (8.6)	27.1 (7.9)	31.4 (12.3)	26.4 (7.8)	42.5 (15.2)	27.5 (0.7)	$F_{(4, 276)}$ =4.48 *p*=0.002
Ethnicity, *n*(%)							
White		90 (38.8)	9 (45.0)	1 (10.0)	3 (75.0)	1 (50.0)	x^2=6.13 *df*=4 *p*=0.14
Black		142 (61.2)	11 (55.0)	9 (90.0)	1 (25.0)	1 (50.0)	

s.d., standard deviation; df, degrees of freedom

Figure 9. *Flow chart documenting how cases were traced and administrative outcomes five years after first contact with mental health services for schizophrenia spectrum psychosis (there are no cases of schizotypal disorder included)*



6.3.2. Core analytic cohort

I successfully traced *n*=245 (86.9%) of the original GAP cohort. Of these, 67.3% were male and 61.1% were of Black ethnicity. There were 239 cases with sufficient information on treatment over the follow up period to determine TR or non-TR status. Eighty (33.5%) of the cases met the criteria for TR and *n*=159 (66.5%) were non-TR. The other 6 (2.4% of the core analytic cohort) cases had not received an adequate trial of antipsychotic medications to allow it to be determined if criteria for TR or non-TR was met.

6.3.3. Predictors of treatment-resistance (TR)

Comparisons in baseline sociodemographic and clinical characteristics between the TR and non-TR groups are presented in **Table 22**. Patients in the TR group were significantly younger on the first presentation to mental health services for first psychotic symptoms ($mean_{years}$=25.0, sd=6.1) when compared to the non-TR group ($mean_{years}$=27.9, sd=8.3) (*t*=2.79, *df*=148, *p*=0.01). The median length of DUP for the TR group was 72 days (IQR=15-368) which was longer but not significantly from the non-TR group (median=40, IQR=5-127) (Mann Whitney *U* test=-1.56, *p*=0.12). There was no significant difference between the mean IQ in the TR group (mean=92.6, sd=13.0) compared with the non-TR group (mean=87.5, sd=16.2) (Mann Whitney *U* test=-1.25, *p*=0.22). The mean premorbid IQ was higher in the TR group (mean=92.8, sd=9.6) compared to those in the non-TR group (mean=88.5, sd=11.0), but this did not reach statistical significance (Mann Whitney *U* test=-1.58, *p*=0.11).

Table 22. *Comparisons in baseline characteristics between the non-treatment resistance (i.e., TR) non- and treatment resistance (i.e., TR) groups. These analyses are limited to first-episode schizophrenia spectrum patients and exclude cases of schizotypal disorder*

Characteristic	Non-TR *n*=159 (66.5%)	TR *n*=80 (33.5%)	Test Statistics		
	Mean (SD)/*n*(%)	Mean (SD)/*n*(%)	t/U/x^2	df	*p*
DUP $_{days}$ Median (IQR)	40 (5-127)	72 (15-368)	-1.56		0.12
Age $_{years}$	27.9 (8.3)	25.0 (6.4)	2.79	237	0.01
Gender					
Female	52 (32.7)	27 (33.7)	0.03	1	0.49
Male	107 (67.3)	53 (66.3)			
Ethnicity					
White ethnic groups	57 (37.7)	30 (39.5)	0.06	1	0.46
Black ethnic groups	94 (62.3)	46 (60.5)			
Living arrangements					
Alone	41 (42.3)	15 (38.5)	0.17	1	0.42
Not alone	56 (57.7)	24 (61.5)			
Relationship status					
Single/separated	78 (80.4)	32 (80.0)	0.003	1	0.56
Stable relationship	19 (19.6)	8 (20.0)			
Education					
no/basic	79 (82.3)	32 (82.1)	0.001	1	0.58
higher	17 (17.7)	7 (17.9)			
Cannabis use					
none/infrequent	75 (67.6)	32 (68.1)	0.004	1	0.55
every day	36 (32.4)	15 (31.9)			
Alcohol intake					
0-14 units week	83 (86.5)	51 (89.5)	0.30	1	0.39
>15 units week	13 (13.5)	6 (10.5)			
Current IQ minus estimated premorbid IQ	1.01 (1.5)	0.1 (2.81)	0.30	67	0.76

SD, standard deviation; df, degrees of freedom; IQR, interquartile range; DUP, Duration of untreated psychosis

Baseline clinical predictors of TR at five-year follow up for the whole sample and stratified by ethnicity and gender are presented in **Table 23**. The severity of psychotic symptoms as measured by PANSS at the time of first contact for psychosis did not predict the risk for TR during the first five years of follow up. Those patients who were defined as TR were more likely to have an early illness onset (<20 years) compared to the non-TR group (OR=2.66, 95% CI=1.31-5.40). Further, there were significant interactions between age at first contact for psychosis with ethnicity (*p*=0.02) and gender (*p*=0.002). Therefore, in addition to exploring the impact of age at first contact in predicting TR in the cohort, I further stratified the analyses by gender and ethnicity. I observed that this relationship between an early age of first contact (<20 year) and TR was significant in cases of Black ethnicity (OR=3.71, 95% CI=1.44-9.56) and in males (OR=3.13, 95% CI=1.35-7.23) independent of confounding factors (**Table 24**).

Table 23. Baseline *clinical predictors of treatment resistance (TR) in a sample with schizophrenia spectrum disorder*

Baseline clinical predictors	Total sample (*n*=245)	
	Non-TR OR (95% CI)	TR OR (95% CI)
[a] Age categories		
>31 years	-	0.58 (0.28-1.20)
26-30 years	-	1.09 (0.54-2.20)
21-25 years	-	0.66 (0.35-1.26)
<20 years	-	2.66*** (1.31-5.40)
[b] Psychopathology		
PANSS total	-	1.01 (0.98-1.04)
PANSS Positive	-	1.02 (0.96-1.09)
PANSS Negative	-	1.01 (0.94-1.10)
GAF Disability	-	0.98 (0.95-1.01)
GAF Symptoms		0.97 (0.93-1.00)
PANSS Lack of judgement & insight	-	1.13 (0.82-1.57)
PANSS Conceptual disorganisation		1.16 (0.90-1.51)

OR, odds ratio; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale, GAF, Global Assessment of Functioning Scale; DUP, duration of untreated psychosis
[a] Adjusted for alcohol use, illicit substance use and living arrangements at follow up
[b] Adjusted for age at first contact, alcohol use, illicit substance use and living arrangements at follow up
*p<0.05, ** p<0.01, *** p<0.001

Table 24. *Age at first contact as a baseline predictor of treatment resistance (TR) in a sample with schizophrenia spectrum disorder stratified by gender and ethnicity*

Baseline clinical predictors	by Ethnicity				by Gender			
	White ethnic group (*n*=90)		Black ethnic group (*n*=142)		Female (*n*=80)		Male (*n*=165)	
	Non-TRS OR (95% CI)	TRS OR (95% CI)	Non-TRS OR (95% CI)	TRS OR (95% CI)	Non-TRS OR (95% CI)	TRS OR (95% CI)	Non-TRS OR (95% CI)	TRS OR (95% CI)
[a] Age categories								
>31 years	-	1.01 (0.31-3.25)	-	0.47 (0.18-1.27)	-	0.63 (0.22-1.80)	-	0.38 (0.12-1.18)
26-30 years	-	1.69 (0.60-4.79)	-	0.82 (0.29-2.29)	-	0.86 (0.23-3.27)	-	1.33 (0.57-3.10)
21-25 years	-	0.43 (0.14-1.30)	-	0.70 (0.29-1.65)	-	1.32 (0.44-3.96)	-	0.49 (0.21-1.11)
<20 years	-	1.60 (0.43-5.87)	-	3.71*** (1.44-9.56)	-	1.92 (0.43-8.60)	-	3.13*** (1.35-7.23)

OR, odds ratio; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale, GAF, Global Assessment of Functioning Scale; DUP, duration of untreated psychosis
[a] Adjusted for alcohol use, illicit substance use and living arrangements at follow up
*p<0.05, ** p<0.01, *** p<0.001

6.3.4. "Clozapine" group vs "met criteria" group

Comparisons in baseline sociodemographic and clinical characteristics between the "Clozapine" group *vs* "met criteria" group are presented in **Table 25**. Among those patients who were defined as TR, *n*=38 TR cases (47.5% of *n*=80 TR group and 15.5% of *n*=245 cases with a diagnosis of schizophrenia spectrum psychosis at study entry) commenced treatment with clozapine; whereas *n*=42 TR cases (52.5% of *n*=80 TR group) met criteria for clozapine (for more details please refer to Chapter 2, section 2.3.6.2.6.- 2.3.6.2.7., ., page 76) but did not commence it. A significantly higher proportion of patients in the clozapine group (91%) lived with family members or friends compared to the "met criteria" group (50%) (x^2=5.58, *p*=0.02). At first contact for psychosis, the clozapine group had exhibited more severe psychopathology (Mann Whitney *U* test=2.05, *p*=0.04) and negative symptoms (Mann Whitney *U* test =2.01, *p*=0.04) than the "met criteria" group. Similarly, the clozapine group also had increased negative symptoms (mean=21.7, sd=9.1) compared to the non-TR group (mean=15.4, sd=6.0) (Mann Whitney *U* test=-2.22, *p*=0.02)

Table 25. *Comparison in baseline socio-demographic and clinical characteristics between "clozapine" group and those who met criteria for clozapine ("met criteria") but did not commence the clozapine during the course of illness*. These analyses are limited to first-episode schizophrenia spectrum patients and exclude cases of schizotypal disorder

Baseline socio-demographic and clinical characteristics	Clozapine *n*=38 (47.5%)	Met criteria *n*=42 (52.5%)	Test statistics		
	Mean (sd)/*n*(%)	Mean (sd)/*n*(%)	t/U/x^2	df	*p*-value
Age $_{years}$	24.7 (5.1)	25.3 (7.4)	-0.41	78	0.68
Gender					
Female	10 (26.3)	17 (40.5)	1.79	1	0.13
Male	28 (73.7)	25 (59.5)			
Ethnicity					
White (all categories)	16 (44.4)	14 (35.0)	0.71	1	0.27
Black (all categories)	20 (55.6)	26 (65.0)			
Living arrangements					
Alone	1 (9.1)	14 (50.0)	5.58	1	0.02
Not alone	10 (90.9)	14 (50.0)			
Relationship status					
Single/separated	9 (81.8)	23 (79.3)	0.03	1	0.62
Stable relationship	2 (18.2)	6 (20.7)			
Cannabis use					
none/infrequent	15 (71.4)	17 (65.4)	0.19	1	0.45
every day	6 (28.6)	9 (34.6)			
Alcohol intake					
0-14 units week	24 (96.0)	27 (84.4)	2.01	1	0.16
>15 units week	1 (4.0)	5 (15.6)			
DUP $_{days}$					
Median (IQR)	33 (14-102)	171 (19-439)	-1.17		0.24
PANSS total	79.1 (16.3)	63.6 (17.7)	2.05		0.04
PANSS Positive	17.8 (6.6)	16.0 (8.2)	0.92		0.36
PANSS Negative	21.7 (9.1)	14.9 (6.2)	2.01		0.04
GAF Disability	51.7 (11.0)	49.3 (16.6)	0.86		0.39
GAF Symptoms	40.0 (13.3)	39.9 (18.4)	0.33		0.74
PANSS Lack of judgement & insight	4.2 (1.8)	3.4 (1.8)	1.07		0.28
PANSS Conceptual disorganisation	2.7 (1.1)	2.2 (1.4)	1.43		0.15

sd, standard deviation; df, degrees of freedom; PANSS, Positive and Negative Syndrome Scale, GAF, Global Assessment of Functioning Scale; DUP, duration of untreated psychosis

6.3.5. "Early-resistance" TR (E-TR) vs "Late-resistance" TR (L-TR) with the non-TR groups

Among those with TR, *n*=55 (69.6% of *n*=79 with TR) were E-TR and *n*=24 (30.4% of *n*=79 with TR) were L-TR. at the time of first contact for psychosis, there were no significant differences in sociodemographic characteristics between the E-TR and non-TR groups, and between the L-TR and non-TR cases (**Tables 26-27**). The E-TR group expressed more severe psychopathology at baseline (mean total PANSS score=72.7, sd=20.6) than the non-TR group (mean total PANSS score=62.7, sd=16.8) (Mann Whitney *U* test=-2.07, *p*=0.04) (**Table 26**). Additionally, patients in the L-TR group were significantly younger at the time of first contact for psychosis ($mean_{years}$=23.7 years, sd=5.1) compared to the non-TR group ($mean_{years}$=27.4 years, sd=8.0), (*t*=2.44, df=81, *p*=0.03) (**Table 27**).

Table 26. *Comparison in baseline socio-demographic and clinical characteristics between non-treatment resistance (i.e. non-TR) group and "early resistance" E-TR. These analyses are limited to first-episode schizophrenia spectrum patients and exclude cases of schizotypal disorder*

Baseline socio-demographic and clinical characteristics	Non-TR *n*=159 (74.3%)	E-TR *n*=55 (25.7%)	Test statistics		
	Mean (sd)/*n*(%)	Mean (sd)/*n*(%)	t/U/x2	df	*p*
Age $_{years}$	27.9 (8.3)	25.6 (6.9)	1.87	212	0.06
Gender					
Female	52 (32.7)	14 (25.4)	101	1	0.40
Male	107 (67.3)	41 (74.6)			
Ethnicity					
White	57 (37.8)	20 (37.7)	0.00	1	0.99
Black	94 (62.2)	33 (62.3)			
Living arrangements					
Alone	41 (42.3)	11 (39.3)	0.08	1	0.83
Not alone	56 (57.7)	17 (60.7)			
Relationship status					
Single/separated	78 (80.4)	23 (79.3)	0.02	1	0.90
Stable relationship	19 (19.6)	6 (20.7)			
Cannabis use					
none/infrequent	75 (67.6)	23 (74.2)	0.05	1	0.52
every day	36 (32.4)	8 (25.8)			
Alcohol intake					
0-14 units week	83 (86.5)	33 (84.6)	0.08	1	0.79
>15 units week	13 (13.5)	6 (15.4)			
DUP $_{days}$					
Median (IQR)	40 (5-127)	59 (10-368)	-0.85		0.40
PANSS total	62.7 (16.8)	72.7 (20.6)	-2.07		0.04
PANSS Positive	15.3 (6.7)	17.9 (8.2)	-1.36		0.17
PANSS Negative	15.4 (6.0)	17.4 (8.5)	-0.71		0.48
GAF Disability	54.4 (20.6)	48.7 (14.8)	1.11	77	0.27
GAF Symptoms	49.0 (27.8)	40.5 (17.3)	1.45		0.15
PANSS Lack of judgement & insight	3.3 (1.7)	3.9 (1.8)	-1.46		0.14
PANNS Conceptual disorganisation	2.1(1.4)	2.6 (1.4)	-1.82		0.07

TR, treatment resistance; sd, standard deviation; df, degrees of freedom; PANSS, Positive and Negative Syndrome Scale, GAF, Global Assessment of Functioning Scale; DUP, duration of untreated psychosis

Table 27. *Comparison in baseline socio-demographic and clinical characteristics between non-treatment resistance (i.e., non-TR) group and "late resistance" L-TR. These analyses are limited to first-episode schizophrenia spectrum patients and exclude cases of schizotypal disorder*

Baseline socio-demographic and clinical characteristics	Non-TR *n*=159 (86.9%)	L-TR *n*=24 (13.1)	Test statistics		
	Mean (sd)/*n*(%)	Mean (sd)/*n*(%)	t/U/x2	df	*p*
Age $_{years}$	27.9 (8.3)	23.7 (5.1)	2.44	181	0.02
Gender					
Female	52 (32.7)	13 (54.2)	4.19	1	0.07
Male	107 (67.3)	11 (45.8)			
Ethnicity					
White	57 (37.8)	9 (40.9)	0.08	1	0.82
Black	94 (62.2)	13 (59.1)			
Living arrangements					
Alone	41 (42.3)	4 (40.0)	0.02	1	0.89
Not alone	56 (57.7)	6 (60.0)			
Relationship status					
Single/separated	78 (80.4)	8 (80.0)	0.001	1	0.98
Stable relationship	19 (19.6)	2 (20.0)			
Cannabis use					
none/infrequent	75 (67.6)	9 (60.0)	0.34	1	0.57
every day	36 (32.4)	6 (40.0)			
Alcohol intake					
0-14 units week	83 (86.5)	17 (100.0)	2.60	1	0.21
>15 units week	13 (13.5)	-			
DUP $_{days}$ Median (IQR)					
PANSS total	62.7 (16.9)	63.5 (13.6)	-0.26		0.80
PANSS Positive	15.3 (6.7)	13.9 (5.9)	0.54		0.59
PANSS Negative	15.4 (6.0)	17.2 (7.2)	-0.73		0.47
GAF Disability	54.4 (20.6)	55.0 (15.3)	-0.08	65	0.94
GAF Symptoms	49.0 (21.8)	37.9 (16.3)	1.27		0.20
PANSS Lack of judgement & insight	3.3 (1.7)	3.2 (1.9)	0.18		0.86
PANSS Conceptual disorganisation	2.1 (1.4)	1.9 (1.1)	0.23		0.82

TR, treatment resistance; sd, standard deviation; df, degrees of freedom; PANSS, Positive and Negative Syndrome Scale, GAF, Global Assessment of Functioning Scale; DUP, duration of untreated psychosis

6.4. Discussion

My main findings are that TR illness was seen in 34% of patients by the end of the 5-year follow-up period after first contact with mental health services, and 70% of the TR patients did not respond to treatment with antipsychotic medications from illness onset. Further, an earlier age of illness onset was strongly associated with TR status by the end of the follow up period. This is consistent with the results of previously published studies indicating that an earlier age of onset is associated with poorer outcomes and lower rates of complete remission in patients with FEP [74, 276]. Although a younger age of illness onset has been previously associated with the emergence of treatment resistance in patients with schizophrenia [277, 278], my study highlights this in a longitudinal study of first episode schizophrenia spectrum psychoses. Cumulatively, these results show that clinicians may need to be more vigilant when treating individuals with a first episode of schizophrenia spectrum psychosis in late adolescence (ages<20) in terms of their response, or lack of it, to initial trials of antipsychotic medications and to be prepared to use clozapine more promptly when a lack of response is evident.

The significant association between the illness onset before the age of 20 and TR was most marked for males and for those of Black ethnicity. The finding that males had an earlier onset of illness in the non-TR group in combination with the younger age of SZ onset in those who eventually develop TR may be indicative of the neurodevelopmental model of the TRS. However, there was no evidence to suggest that the estimated deterioration in IQ scores was greater in the TR group compared to the non-TR group. Similarly, my results did not indicate that environmental risk factors were more prevalent in the TR group. Thus my findings do not provide support for a neurodevelopmental pre-eminence in the TR group.

It is noteworthy that there are a number of other factors that have been shown to play an important role in risk for treatment resistance and in general lack of response to treatment with antipsychotic medications in patients with schizophrenia, such as urbanicity [279] and genetic risk factors [280] [281] [282] that have not been examined in this study. Further, it has been suggested that major depressive disorder in comorbidity with schizophrenia was a predictor for TRS[283]. Cognitive symptoms have also been suggested to be associated with poor response to antipsychotics[283]. However, I did not examine these risk factors in my sample in association with TRS and its possible two types as it was beyond of the aims of my PhD. I

hope future research on treatment resistance and its possible subtypes can expand to include all of these additional potential risk factors.

6.4.1. Early resistance TR (E-TR) & Late resistance (L-TR)

Of the TR group, 70% displayed unremitting symptoms from the time of first antipsychotic treatment. This finding is mirrored in the AESOP-10 year follow up study of FEP cases where it was shown that 84% of those with TR were resistant from illness onset[284], even though the sample employed in the AESOP-10 study was not specific to schizophrenia spectrum psychoses. Cumulatively, these findings indicate that this course of illness is not associated with prior antipsychotic use but rather raises the possibility that it may be a distinctive schizophrenia subgroup. This assumption is further supported by evidence indicating the biological differences between treatment resistant and treatment responsive schizophrenia[285, 286]. Further, in this study, 30% of those with TR initially responded to antipsychotic medications before developing late treatment resistance. One feasible explanation for this finding is that the loss of antipsychotic response may be due to the emergence of dopamine super-sensitivity in these patients.

6.4.2. Access to clozapine

Clozapine was commenced in less than half of those who met criteria for TR over the course of the 5-year follow up. Those who were commenced on clozapine were more likely to exhibit more severe psychotic symptoms and increased negative symptomatology at baseline when compared to those who 'met-criteria' for clozapine use but had not commenced it. These results may indicate that a more florid psychosis may be a likely factor in decision-making for the earlier use of clozapine in TR. Further, my results showed that those patients who were started on clozapine were significantly more likely to be living at home with family, compared to those who 'met criteria' for TR potentially. This in turn may be indicative of reluctance to initiate treatment with clozapine in patients who are perceived to have lack of family support or have unstable living arrangements.

6.4.3. Methodological considerations

The main limitations of the present study include the relatively small population of female patients and the lack of a robust measure of medication adherence, which may have affected the association with meeting the criteria for TR [287]. The rate of TR reported by the end of the 5-year follow up is relatively high. This may be due to the fact that a higher proportion of the original patients employed in this study were recruited from inpatient rather than community settings. Specifically, a higher proportion recruited from inpatient settings might indicate a greater clinical need for more intensive treatments than those who were managed in the community setting (though who were not recruited to this study). This is particularly relevant as the threshold for psychiatric hospital admission in London (UK) is higher than many other settings.

6.5. Summary and concluding remarks

Clozapine remains the only evidence based antipsychotic for TR in patients with SZ. The ability to predict which patients with first onset of schizophrenia would subsequently meet criteria for TR could help to reduce or diminish the severe functional disability which in turn may ensue if TR is not recognised and treated correctly. In this study I utilised *n*=245 first-episode schizophrenia spectrum patients and tested the relationship between baseline demographic and clinical characteristics and the emergence of TR by the end of the 5-year follow up period. Additionally, I assessed associations with early- and late- onset TR and non-TR, and differences between those TR patients treated with clozapine and those who met NICE criteria for clozapine but had not commenced.

The results indicate that an early age (i.e., >20) is associated with an increased risk for onset of TR during the first five years, particularly in male patients and patients of Black ethnicity. Over 70% of the TR group presented with a treatment resistant picture at illness onset. I did not find evidence suggesting that social factors and premorbid functioning were associated with the emergence of TR during the course of illness. These findings reinforce the case for early assessment of treatment resistance in first episode schizophrenia spectrum patients so that clozapine may be considered and introduced promptly as a third line treatment in first episode schizophrenia. Future studies with larger samples are required to replicate and progress this important area of clinical prediction.

CHAPTER 7 GENERAL DISCUSSION

7.1. Overview of the findings and their implications

In this thesis I set out to investigate pathways to care, and longitudinal clinical and social outcomes in patients with first episode psychosis (FEP) who were recruited as part of the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) Genetics and Psychosis (GAP) study as well as EUropean network of national schizophrenia networks studying Gene-Environment interaction (EU-GEI) study and presented to the psychiatric services of the South London and Maudsley (SLaM) National Health Service (NHS) Foundation Mental Health Trust. In this chapter I will outline my main findings and their implications for the wider clinical or research practices in the light of methodological limitations.

7.1.1. Study 1: Pathways to care in first episode psychosis patients: Looking back at use of prodromal services

7.1.1.1. Overview of main results

This is the first study to have examined the differences in pathways to care and clinical presentation between heterogeneous groups of patients with FEP resident in inner city deprived areas of South London. The results showed that 4.1% of patients presenting to mental health services with FEP had previously presented to the ARMS services during the prodromal phase of psychosis and subsequently transitioned to clinical psychosis. This sub-group of patients was significantly younger at the time of first contact with mental health services compared to the FEP patients without prior contact with the ARMS services. This finding may be indicative of the ability of the ARMS services to detect at risk patients earlier compared to the standard early intervention services for FEP. However, as the ARMS services have established a cut-off point in age for accessing the services to be 35 year old or lower, individual with a later age of onset would not have been in contact with the prodromal teams. This in turn would ensure that the prodromal teams always deal with patients who are younger at the age of first contact compared to the standard services for psychosis.

Although the interval between the first onset of symptoms and initiation of treatment was shorter in those attending the ARMS services compared to those referred to conventional services, the overall difference in DUP between these two groups did not meet the standard threshold for statistical significance. DUP is dependent on a number of factors that need to be examined in order to understand this result: 1) *sources of referral* to mental health services [41, 245, 249 41]; 2) *help-seeking behaviours* [248, 249]; 3) *mode of onset* of first psychotic symptoms [225, 226, 288]., and 4) *absence of a consensus definition of DUP*. I will examine each of these points in light of my findings.

7.1.1.2. DUP and Sources of referral to mental health services

I found that 77% of all referrals to the ARMS services were made by health professionals such as local GPs and other health workers. In contrast, 45% of the FEP without a prior contact with the ARMS teams came under care of mental health services via emergency services and 18% were referred by criminal justice agencies, such as police and courts. These results show that a substantial proportion of young individuals with an early onset of psychosis do not seek help [248, 249], and may not even be registered with a GP. Therefore, they will not be detected by the prodromal services or other services until the involvement of police or emergency services becomes inevitable. Moreover, considering that GP attendance is associated with prolonged DUP [41, 245, 249], while the emergency medical services and criminal justice agency are associated with substantially shorter DUP [41], it may be that the DUP would have remained significantly different were the pathways to care the same between the groups.

7.1.1.3. DUP and Help-seeking behaviours

Identification of individuals with subclinical psychotic experiences is heavily reliant on help-seeking behaviours. The likelihood of help-seeking is dependent on the awareness and insight into the earliest manifestations of psychotic symptoms, and even more so on the availability of supportive families and strong social networks around young individuals who are at high risk [226]. Indeed, in my sample at the time of first contact with mental health services a higher proportion of the FEP patients without prior contact with the ARMS services did not have a stable accommodation and lived alone compared to those FEP patients who had prior contact with prodromal teams. The age of illness onset is another important factor that may have an impact on whether the patients would seek help or not.

For example, it has been shown that young individuals with onset of psychosis between 16-29 years of age are less likely to engage in help-seeking behaviours compared to those individuals who had onset of first psychotic symptoms within 30-65 years age category [226]. Therefore, many young individuals who qualify for care of prodromal services would not have been under their radar straight away causing a longer DUP than expected. It has been previously suggested that individuals of non-white British ethnicity were reluctance to seek help during a mental health crisis [269, 270], which might have been linked to distrust of psychiatric services [271], lack of insight into mental health difficulties [272] and language barriers [270]. In this study I have shown that a significant proportion of FEP patients who did not have prior contact with the prodromal teams were non-UK born individuals. This is an important factor to consider when trying to shed some light on the unexpectedly longer DUP observed in this study.

7.1.1.4. DUP and Mode of onset

The vast majority of the prodromal group had an insidious mode of onset, which is characterised by a lack of clear differentiation between premorbid personality and onset of psychosis[289]. Not surprising therefore, this type of symptoms onset has been shown to be associated with considerable delays in initiation of treatment after first onset of psychotic symptoms [226]. With slower onset of first symptoms it may be difficult to distinguish the first indicators of the illness from other motivational or developmental difficulties [245], prompting the individuals to re-adjust their lifestyle in attempts to minimise the disruption or distress associated with the illness rather than seek help [226]. Similarly, members of their families or close friends may be less likely to encourage these individuals to help-seek when the onset of symptoms is spread over a long period [226]. My results indicate that some people have an onset that is rapid and severe while in others have onset that is so insidious that they escape the notice of the prodromal services

7.1.1.5. No consensus definition of DUP [5]

Currently there is no consensus definition of DUP. This, at least partially, may be due to still existing challenges of differentiating between what constitutes onset of psychotic symptoms,

[5] This section was published in David, AS and Ajnakina, O (2016). Psychosis as a continuous phenotype in the general population: The thin line between normality and pathology. *World Psychiatry*, 15(2):129-30. doi: 10.1002/wps.20327.

which can then be used as a marker for onset of the period of untreated psychosis and the onset of the actual psychotic disorder. The claim that ARMS services reduce the DUP in comparison to standard clinical services for psychosis [244] is critically dependent on whether the time between the earliest report of symptoms and the early intervention services is taken as the DUP or, whether the beginning of DUP is 'reset' after such an intervention unless or until the individual develops their first episode of full-blown psychosis. Another approach that would help shed some light on what constitutes DUP is to clearly differentiate between the duration of prodromal period which is defined as the period from the first unspecific symptoms related to psychosis to the first continuous (present most of the time) psychotic symptom [290] and the actual DUP. This method would enable one to highlight whether and how much the prodromal services benefit the patients before they make the transition to the FEP and how lasting these benefits are over the subsequent course of illness. Unfortunately I was unable to examine this in the present study.

7.1.1.6. *Do prodromal services provide care to those who might not have access to care otherwise?*

My results highlighted that ~75% of those patients who had prior contact with the prodromal services before coming to the standard services for FEP were already fully psychotic at the time of the contact with the ARMS services. As this group of patients did not significantly differ from the FEP who did not have prior contact with the prodromal team, I concluded that the prodromal services do not appear to be providing additional functions by detecting individuals with FEP who otherwise would not have had access to mental health services.

7.1.1.7. Conclusion

This preliminary work suggests that when we look back on the journey that first episode psychosis patients took before arriving at the standard clinical services we find that very few come via prodromal services. This suggests that the scope for reducing or postposing the onset of psychosis may still be limited. Much of the work of the ARMS services, and by implication similar prodromal programmes, appears to be spent dealing with people who either will not develop psychosis, or are already experience a first episode of psychosis. While the latter signifies an appetite for a variety of flexible services to care for people with early psychosis, it highlights the greater challenge of providing care for people before they develop psychosis and to therefore prevent it or catch it early. These findings also imply that

research based on the view that high-risk participants recruited through the ARMS services captures a process or phase in the illness that affects the majority of FEP patients may possibly be questioned.

7.1.2. Study 2: Symptom dimensions versus DSM-IV diagnostic categories as predictors of time to first remission in first-episode psychosis during a 4-year follow-up

7.1.2.1. Overview of main results

In this study I showed that the positive, excited and disorganised/concrete dimensions of psychosis are important predictors of time to first remission in patients with FEP. In terms of diagnostic categories, I found that the diagnosis of schizophrenia was associated with a longer time to first remission. I did not find evidence to support my hypothesis that the psychosis symptom dimensions were superior to traditional diagnostic categories in predicting time to first remission. Instead, the results highlighted that the combination of baseline categorical diagnosis of schizophrenia with these five symptom dimensions produced the best model fit. These are novel findings that may serve as markers indicative of those subgroups of patients with FEP who will take substantially longer to remit within four years after first contact with psychiatric services.

7.1.2.2. *Implications for classification*

The significance of these results is two-fold. First, they may have important implications for clinical practice by laying a foundation for integrating symptom profiles into treatment planning in a manner that is generalisable, but sensitive to differences among individual patients. Secondly, they demonstrate that in considering the categorical and dimensional approaches together would provide greater insights into patients' need for care and treatment response. With additional evidence this may influence future classification systems. My findings also suggest that it was unfortunate that symptom dimensions were relegated to an Annexe within the DSM-5.

7.1.2.3. Conclusion

There is currently a greater focus on meaningful and practically applicable outcomes of psychotic disorders with symptomatic remission being accepted as one of the best indicators of treatment efficiency and response. There has recently been a move towards dimensional approaches to psychosis and I was keen to build on previous research which highlighted that combining dimensional measures with categorical diagnoses is more informative in determining the causes of psychosis than considering them separately [218]. I was also keen to build on previous research which highlighted that combining dimensional measures with categorical diagnoses is more informative in determining the causes of psychosis than considering them separately[218].

These results indicate that the use of a combination of the positive, excited and disorganised/concrete dimensions of psychosis with the traditional diagnostic category of schizophrenia provides a more robust prediction of the length of time that it takes for patients to respond to treatment after the first contact with mental health services for psychosis, rather than applying either of these two approaches separately. Therefore, the clinical care for patients with FEP would be best served by supplementing the schizophrenia diagnosis with symptom dimension scores when predicting delayed treatment response as measured by time to first remission. The results of this study need, of course, to be replicated in other prospective cohorts.

7.1.3. Study 3: Patterns of illness and care over the 5 years following onset of psychosis in Black African, Black Caribbean and White British patients

7.1.3.1. Overview of main results

Over the first five years of follow up after first contact with mental health services, 63.1% of my overall sample reported symptomatic remission and 28.4% met criteria for symptomatic recovery at least once. The rates of remission and recovery that I identified in my research are confident with the studies that have investigated clinical longitudinal outcomes in FEP patients. Specifically, as outlined in the **Table 1** (page 29) there are 57 studies published to date reporting on remission rates and 39 studies reported on recovery rates, with 18 studies

reporting on both remission and recovery, with a pooled rate of remission is 59.3% and for recovery is 39.4%.

The overall clinical illness course was quite homogenous across White British, Black African and Black Caribbean ethnic groups. This stands in contrast to the pattern of care that patients from Black African and Black Caribbean ethnic backgrounds received compared to their White British counterparts during the follow up period. Patients of Black African ethnic group were at a greater risk to be re-admitted, to be admitted under MHA or have police involved prior to or during a re-admission at least once during the 5-year follow up compared to their White British counterparts. Further, patients of Black African ethnicity were at a greater risk of multiple compulsory admissions and police involvement during admissions over the follow up period than patients of White British ethnicity. Similarly, patients of Black African and Black Caribbean ethnicity were at an elevated risk to have a higher number of re-admissions to a psychiatric ward than their White British counterparts. All of these results were independent of differences in living arrangements, relationship status and substance use during the course of follow up between these ethnic groups.

Additionally, I found that the proportion of unemployed increased in White British and Black African ethnic group by the end of the follow up period. While it is common for individuals with psychosis to struggle to develop or maintain stable relationships [273], there was an increased proportion of single individuals in the Black African and Black Caribbean ethnic group compared with White British group. Cumulatively these findings suggest that patients of Black ethnicity become increasingly socially excluded as their illness progress.

7.1.3.2. Conclusion

Ethnic disparities in mental health outcomes have become an area of concern. In this study I examined the longitudinal clinical outcomes and patterns of treatment in patients with FEP of White British, Black African and Black Caribbean ethnicity over a 5-year course of illness. The results of this study demonstrate that differences remain in patterns of care among those of Black African, Black Caribbean and White British patients who are resident in London during the first five years after first contact with mental health services for psychosis. The longitudinal trajectory of psychosis in patients of Black ethnicity is characterised by longer inpatient stays, higher rates of compulsory admissions and increased instances of police involvement during or shortly before a re-admission to a psychiatric hospital compared

with patients of White British ethnicity. The observed pattern of care in Black ethnic groups was not reflected in their overall functional disability and illness severity in the due illness course or likelihood to report either remission or recovery during the follow up period. The prognosis is also still poor in terms of social functioning and isolation among Black ethnic groups during their illness. Further study is required to establish whether these differences reflect social or clinical differences between ethnic groups. Nonetheless, our findings reiterate a greater need for action in health systems and social policy to challenge and reduce these disparities.

7.1.4. Study 4: Clinical predictors of treatment resistance in first episode schizophrenia & Two distinct patterns of treatment resistance

7.1.4.1. Overview of main results

Treatment resistance (TR) was seen in 35% of patients with first episode schizophrenia spectrum disorders by five years follow-up; an earlier age of onset of psychosis (<20 years old) was strongly associated with TR. This association was specific to patients of male gender and for those of Black ethnicity. These findings reinforce the case for early assessment of treatment resistance in first episode patients so that clozapine may be considered and introduced promptly as a third line treatment in first episode schizophrenia.

7.1.4.2. Two types of TR: Early-resistant and Late-resistant TR

The finding that 23% of the total population met the criteria for TR from illness onset indicates that this course of illness may not be associated with prior antipsychotic use and raises the possibility that it may be a distinctive and homogenous schizophrenia subgroup. This is in line with evidence that there may be biological differences between treatment resistant and treatment responsive schizophrenia[285, 286]. This finding also mirrors the rate of 20% who displayed 'chronicity' from illness outset in a FEP population [50], though is higher than a previous finding of 10% of FEP cases found to have shown not to respond to antipsychotic medications at the end of the first year of treatment [291].

Further, my finding that 70% of the TR group displayed early treatment resistance is similar to an earlier study in established schizophrenia, which identified that over half of patients

with ‘poor outcomes’, remained psychotic from illness onset [292]. The high rates of early resistance of those with TR in this population is an important finding and should be viewed in relation to the delay in clozapine use which still exists in clinical practice [214]. The remaining 30% of the treatment resistant group gradually transitioned to TR having responded to treatment at the start of the illness. One possibility is that the loss of antipsychotic response could be due to the emergence of dopamine receptor super-sensitivity in these patients. Dopamine super-sensitivity is postulated to occur due to upregulation of dopamine receptors and neural adaptation[293, 294]. Cumulatively, these findings indicate that two distinct patterns of TR may exist in patients, with the majority displaying TR from the onset and a smaller subset of patients developing TR after periods of relapse.

7.1.4.3. Implications for clinical practice

Increasingly, cases of first episode schizophrenia spectrum disorders in higher-income countries are managed within dedicated early intervention and first episode psychosis services. However, delays remain in the initiation of clozapine [214]. In this study of a first episode schizophrenia spectrum psychosis cohort, I found that 70% of those with TR would have been most appropriately treated with clozapine at an early stage of their presentation. This suggestion is further strengthened by evidence that early treatment with clozapine is effective [295] and that worse outcomes are seen with a delayed use of clozapine [296, 297]. Thus, there is a need for a greater awareness and appreciation within FEP services that early resistance to antipsychotic medication is a not uncommon phenomenon.

7.1.4.3. Accessing Clozapine: Current practice and future directions

Clozapine was commenced in less than half of those with TR over the course of the 5 years follow up. Those who were commenced on clozapine in this study were more likely to exhibit more severe psychotic symptoms and increased negative symptomatology at baseline when compared to those who ‘met-criteria’ for clozapine use but had not commenced it during the period of the follow up. These findings in turn indicate that a more florid psychosis may be a likely factor in a clinician’s decision for the earlier initiation of clozapine in TR. Another significant finding in relation to practice and clozapine initiation was that those started on clozapine were significantly more likely to be living at home with family compared to those who ’met criteria’ for clozapine in patients with TR. This may be indicative of a possibility that clozapine treatment is restricted for some who meet criteria for TR due to a perceived lack of

family support or unstable living arrangements. An alternative explanation may be that patients living with family are more likely to take their clozapine, whereas those living alone are often given a depot instead. These factors should prompt a consideration for the provision of more dedicated hospital and community facilities to allow for the successful completion of the early stages of clozapine use with adequate supervised accommodation provided as required. There is some evidence that such an approach is effective in increasing access to clozapine[298].

7.1.4.4. Conclusion

Cumulatively, these findings of this study reinforce the case for early assessment of treatment resistance in patients with first episode schizophrenia so that clozapine may be considered and introduced promptly as a third line treatment. The identification of the two types of TRS may imply that there may be two distinct mechanisms responsible for onset of treatment resistant in patients with schizophrenia. Future studies with larger samples are required to replicate and progress this important area of clinical prediction.

7.2. Methodological considerations

7.2.1. Strengths

7.2.1.1. Sample

The sample utilised in this thesis was a well-characterised sample of first onset patients presenting for the first time with psychosis. Therefore, the findings reported here are not likely to be confounded by chronicity of illness or prolonged medication use [25, 49].

7.2.1.2. Comparability of the results.

The results reported in this PhD thesis have produced findings, which are directly comparable with other research conducted in this field. Specifically, WHO Life Chart measure for retrospective data collection that, in addition to having been shown to be a

reliable scale, has been used across a number of studies conducted either in the same geographical region[74] as my thesis or in other countries in Europe [109]. Similarly, I employed the operationalised definition of remission (Study 2 and 3) that has previously been utilised in earlier studies conducted in the same geographical region[74, 240]. Further, the five factor model of psychosis symptoms employed in the Study 2 was selected for being a consensus model derived from existing studies [26] that has been shown to be optimal for use in FEP samples [27]. Cumulatively, this will facilitate the comparability of my results with those obtained in future studies.

7.2.1.3. Duration of follow up.

Current the evidence suggests that the first 3 to 5 years of illness course constitutes the 'critical period' of treatment efficacy[56], beyond this period, the level of sustained disability endures into the long term [206]. Accordingly, in this thesis I focused on the first four (Study 2) and five (Study 3, 4, 5) years of illness after first contact with mental health services for psychosis. Therefore, the results reported in this thesis may have captured the most informative outcomes of illness progression across three major ethnic groups resident in the UK.

7.2.1.4. Drop-out rate

According to the earlier studies that I have presented in **Table 1** and **3**, the current average drop-out rate is 28% across all identified longitudinal studies with an average length of follow up of 5 years[17, 84, 116, 120, 122, 131, 134, 299]. However, the drop-out rate in my theses is 18%, which is considerably lower compared to previous research. Additionally, of this 18% who dropped out from the study during the 5-year follow up period, I established the whereabouts, deaths and emigration status of 7.7% patients. Thus, the cumulative drop-out rate in my sample was 10.3%. This in turn ensures that any potential bias that might have risen due to the non-random loss of information that is inherent to longitudinal study design was kept to the minimum.

7.2.2. Limitations

7.2.2.1. Longitudinal study design

Generally, longitudinal study design tends to suffer from selection bias due to the non-random loss to follow-up. I have made considerable efforts to minimise any potential bias by establishing the whereabouts, deaths and emigration status for 89.7% of the original GAP sample. I have also conducted comparative statistical analyses comparing patients with the information available at followed up and those patients who were lost to follow up. I did not find evidence to suggest attrition bias present in my sample.

7.2.2.2. Using clinical notes for data collection.

It may be argued that collecting information on outcome from clinical records may not produce reliable data. For example, for the purposes of determining the rate and duration of remission from clinical records, treating clinicians might not always have recorded in the notes when symptoms were present and thus in some cases patients may have been classified inaccurately as remitters. Nonetheless, there is evidence suggesting that remission is remarkably stable and does not differ depending on the use of more stringent criteria such as the RSWG, the use of broader criteria (e.g., if defined as patients being asymptomatic & attaining pre-morbid functioning sustained for ≥6 months), nor whether it was based on face-to-face interviews or clinical records[6]. Besides, a similar argument can be applied to prospective study designs. Indeed, the validity and reliability of information obtained from face-to-face interviews after years of exposure to treatments with antipsychotic medications and distress that are all associated with the prolonged course of the illness may also be questioned. It is noteworthy that the electronic clinical notes are the primary clinical recordkeeping system in the South London and Maudsley NHS Foundation Trust which complies with national frameworks such as the Care Programme Approach with the dates, times, contacts and interventions and progress with the treatments explicitly documented. It may therefore be argued that the method for obtaining information on

[6] These findings are based on the meta-analyses of remission and recovery rates in FEP, including diagnostic subgrouping, and moderators of remission and recovery that is currently in preparation for submission by John Lally,* Olesya Ajnakina,* Brendon Stubbs, Robin M Murray (in preparation). Remission and recovery from first-episode psychosis in adults: A systematic review and meta-analysis of long term outcome studies

outcomes may be at least as accurate, or perhaps even more so, as the face-to-face interviews.

Further, following up patients based on their electronic records may imply that those patients who were successfully traced tended to have poorer outcomes or at least a greater need for care as they were still in contact with mental health services at the end of the follow up period compared to those patients who dropped out from the study during the follow-up period. However, this criticism may be not applicable to my study as the vast majority of the patients (~82%) were still under care of mental health services at the end of the follow up period; though it is important to acknowledge that I do not know the nature and severity outcomes of those ~18% patients who were lost to follow up.

7.2.2.3. Underestimated rate of followed up true FEP cases?

Because young individuals and ethnic minorities with an early onset of psychosis may be less likely to be registered with GPs and thus come under the radar of mental health services [173, 174,250], the rate of FEP cases that I have followed up during my PhD may be underestimated.

7.2.2.4. Utilisation of ethnic categories

Another limitation to this thesis centres around the utilisation of ethnic categories which are often not very precise [300]. The use of broad ethnic categories can obscure more subtle variations within the groups.

7.2.2.5. Generalisability of the results.

It is important to note that around 85% of the patients were recruited to the original GAP study from inpatient units; while a substantially smaller proportion of patients was recruited from community based mental health settings. This may imply that the sample represented more severe FEP cases from the start. Therefore, the results reported in this thesis could not be generalised to the general patient population. However, there were no significant differences in mean total PANSS scores (inpatients: 64.1 (sd=16.4) *vs* outpatients: 61.9

(sd=18.9) (Mann Whitney *U* test=0.934, *p*=0.35) and negative PANSS scores (inpatients: 15.5 (sd=6.6) *vs* outpatients: 16.1 (sd=5.8) (*t*=-0.39, *p*=0.70) between those recruited from an inpatient setting and those from a community setting. Though inpatients had significantly increased mean positive PANSS scores (mean=16.2, sd=6.6) compared to those recruited from community settings (mean=13.2, sd=5.8; *t*=2.34, *p*=0.02). Nonetheless, the increased proportion of patients who were inpatients at the study entry, and the recruitment from clinical services rather than by population screening or other methods may imply that some of the clinical outcomes examined in this thesis, such as the rate of treatment resistance identified, may be overestimated.

7.3. Future directions

There are two approaches that can be taken in order shed some light on why psychotic disorders are marked by heterogeneity in terms of clinical presentation [4] and outcomes and how best to predict longitudinal outcomes that in turn would provide guidance to the clinicians on the best intervention strategies to pursue based on an individual's profile across a set of risk factors[301].

7.3.1. Polygenic underpinning of longitudinal outcomes

When trying to disentangle the reasons for the diversity in outcomes and treatment response in patients with first episode psychosis a special consideration should be given to the genetic nature of psychotic disorders, especially schizophrenia. Although many schizophrenia cases are sporadic, around 80% of the variance in liability to this disorder can be attributed to the additive genetic factors [302]. It has now been recognised and acknowledged that schizophrenia is a polygenic illness [303]. Accordingly, a combination of hundreds of thousands of common variants with an effect that would not have any predictive power individually simultaneously contributes to an overall risk to this illness [304]. It has been shown that up to ~35% of genetic liability to schizophrenia was captured by summed common variants (this approach has become known as polygenic risk score for schizophrenia (PRS-SZ) [305])[306]. The ultimate goal of PRS-SZ approach is to identify an individual genetic risk for specific outcomes, such as onset of FEP, or likelihood to respond to a specific treatment. To-date, the PRS-SZ approach has been applied to only a narrow range of disciplines within aetiology of this complex illness, focusing primarily on cognition[307 308 309] and baseline symptom dimensions[310 311 312 313] . There are tree studies which investigated whether PRS-SZ was a good

prognostic tool to use for prediction of response to antipsychotic medications; thigh the results to support this were mixed[282] [281] . More importantly, no studies have tested potential associations between the PRS-SZ and longitudinal outcomes such as response to treatment after first contact with mental health services.

Knowing what groups of patients will have a genetic predisposition for poorer outcomes over the course of illness will lay a strong foundation for the developing of preventive strategies based on an individual genetic loading for the illness. Therefore, future research should aim to examine whether there is significant associations between the PRS-SZ and some of the outcomes that I tested in this thesis over the illness course.

7.3.2. Machine Learning (ML) to predict outcomes on individual levels

While in the present thesis I have outlined an illness trajectory of psychosis starting from the at-risk-mental health to transition to first episode psychosis and finishing with onset of treatment resistance after the first five years of the illness, I did not examine the predictors for these outcomes on an individual level. Thus, if a person came seeking help for first episode psychosis on the basis of my findings all I could tell would have been that on average they may remit within 4 months and never have another episode, or they have 34% of chance to develop chronic and treatment-resistant illness, but there was no way to predict which category they belong to. In the future, I would like to do just that employing machine learning and statistical learning techniques.

Machine learning (ML) methods are designed to provide the best estimate of an outcome in an individual from multiple predictors. These methods use a training dataset to learn from relationships between predictors and outcomes which are then validated in a test dataset to establish how well they predict an outcome in an independent sample[314]. Although ML methods were criticised for being a “black box” as these methods do not provide explanations for why particular variables were selected as predictors of the outcomes, they are power tools for risk prediction at an individual level[314]. Therefore, I propose that the outcomes that I focused on this this thesis, such as remission and services use, should be examined with ML techniques. These results of these potential studies may lay a foundation for a risk calculator that may provide guidance to the clinicians to pursue more appropriate intervention strategies based on an individual’s profile across a set of risk factors.

7.4. Concluding remarks

In this thesis I looked back pathways to care to see how patients came under attention of mental health services, and I looked forwards to investigate the trajectory and different outcomes of the illness over the first 4 to 5 years after patients came in contact with mental health services for psychosis. The main conclusion that I can draw when looking back is that it is still challenging to identify individuals who are at high risk for onset of first episode psychosis and to therefore prevent it or catch it early. When looking forwards, it becomes evident that it was unfortunate that symptom dimensions were relegated to an Annexe within DSM-5 as I showed that the use of a combination of five symptom dimensions and the traditional diagnostic category of schizophrenia provides a more robust prediction of the length of time it takes for patients to respond to treatment as was measured by time to first remission. I also showed that the differences still remain in longitudinal service utilisation for those FEP patients of Black ethnicity resident in London. Finally, my findings reinforce the need for earlier assessment of treatment resistance in first episode patients so that clozapine may be considered and introduced promptly as a third line treatment in first episode schizophrenia. I hope this PhD thesis will service as an encouragement to conduct more detailed and hypotheses-driven research in the field of longitudinal outcomes and FEP to establish the basis for risk prediction, improving the available services and promoting equality of care throughout the illness course.

REFERENCES

1. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet. 2012; **13**(8): 537-51.
2. Mellor CS. First rank symptoms of schizophrenia. I. The frequnncy in schizophrenics on admission to hospital. II. Differences between individual first rank symptoms. Br J Psychiatry. 1970; **117**(536): 15-23.
3. Crow TJ. Molecular pathology of schizophrenia: more than one disease process? Br Med J. 1980; **280**(6207): 66-8.
4. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res. 2009; **110**(1-3): 1-23.
5. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. Lancet. 2007; **370**(9590): 859-77.
6. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007; **64**(10): 1123-31.
7. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophr Bull. 2004; **30**(2): 279-93.
8. Organization WH. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.: World Health Organization: Geneva; 1992.
9. Association AP. Diagnostic And Atatistical Manual of Mental Disorders-IV edition Washington, DC; 1994.
10. McGlashan TH. Eugen Bleuler: centennial anniversary of his 1911 publication of Dementia Praecox or the group of schizophrenias. Schizophr Bull. 2011; **37**(6): 1101-3.
11. Costello CG. Research on symptoms versus research on syndromes. Arguments in favour of allocating more research time to the study of symptoms. Br J Psychiatry. 1992; **160**: 304-8.
12. Kumar A, Khess CR. Factor analysis of positive and negative syndrome scale in schizophrenia: An exploratory study. Indian J Psychiatry. 2012; **54**(3): 233-8.
13. Kay SR, Sevy S. Pyramidical model of schizophrenia. Schizophr Bull. 1990; **16**(3): 537-45.
14. Bell MD, Lysaker PH, Beam-Goulet JL, Milstein RM, Lindenmayer JP. Five-component model of schizophrenia: assessing the factorial invariance of the positive and negative syndrome scale. Psychiatry Res. 1994; **52**(3): 295-303.
15. Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. J Psychiatr Res. 2013; **47**(6): 718-25.
16. Van Os J, Gilvarry C, Bale R, Van Horn E, Tattan T, White I, et al. A comparison of the utility of dimensional and categorical representations of psychosis. UK700 Group. Psychol Med. 1999; **29**(3): 595-606.
17. van Os J, Fahy TA, Jones P, Harvey I, Sham P, Lewis S, et al. Psychopathological syndromes in the functional psychoses: associations with course and outcome. Psychol Med. 1996; **26**(1): 161-76.
18. Frances A. Whither DSM-V? Br J Psychiatry. 2009; **195**(5): 391-2.
19. Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. World Psychiatry. 2013; **12**(2): 92-8.
20. Allardyce J, Suppes T, Van Os J. Dimensions and the psychosis phenotype. Int J Methods Psychiatr Res. 2007; **16**(1): S34-40.
21. Vassos E, Di Forti M, Coleman J, Iyegbe C, Prata D, Euesden J, et al. An Examination of Polygenic Score Risk Prediction in Individuals With First-Episode Psychosis. Biol Psychiatry. 2016; **6**(16): 32664-6.
22. Jones HJ, Stergiakouli, E., Tansey, K. E., Hubbard, L., Heron, J., Cannon, M., Holmans, P., Lewis, Linden, G., D. E. J., Jones, P. B., Smith, G. D., O'Donovan, M. C., Owen, M. J., Walters, J.T.,

Zammit, S. Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population. JAMA Psychiatry. 2016.
23. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. A new five factor model of schizophrenia. Psychiatr Q. 1994; **65**(4): 299-322.
24. Lancon C, Aghababian V, Llorca PM, Auquier P. Factorial structure of the Positive and Negative Syndrome Scale (PANSS): a forced five-dimensional factor analysis. Acta Psychiatr Scand. 1998; **98**(5): 369-76.
25. Emsley R, Rabinowitz J, Torreman M. The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. Schizophr Res. 2003; **61**(1): 47-57.
26. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr Res. 2012; **137**(1-3): 246-50.
27. Langeveld J, Andreassen OA, Auestad B, Faerden A, Hauge LJ, Joa I, et al. Is there an optimal factor structure of the Positive and Negative Syndrome Scale in patients with first-episode psychosis? Scand J Psychol. 2013; **54**(2): 160-5.
28. Fusar-Poli P, Byrne M, Badger S, Valmaggia LR, McGuire PK. Outreach and support in south London (OASIS), 2001-2011: ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. Eur Psychiatry. 2013; **28**(5): 315-26.
29. Yung AR, Stanford C, Cosgrave E, Killackey E, Phillips L, Nelson B, et al. Testing the Ultra High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. Schizophr Res. 2006; **84**(1): 57-66.
30. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res. 2003; **60**(1): 21-32.
31. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry. 2012; **69**(3): 220-9.
32. Ruhrmann S, Schultze-Lutter F, Klosterkotter J. Early detection and intervention in the initial prodromal phase of schizophrenia. Pharmacopsychiatry. 2003; **36**(3): S162-7.
33. Hartmann JA, Yuen HP, McGorry PD, Yung AR, Lin A, Wood SJ, et al. Declining transition rates to psychotic disorder in "ultra-high risk" clients: Investigation of a dilution effect. Schizophr Res. 2016; **170**(1): 130-6.
34. Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry. 2000; **177**: 511-5.
35. Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. Arch Gen Psychiatry. 2006; **63**(3): 250-8.
36. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. Schizophr Bull. 1996; **22**(2): 283-303.
37. Power P, McGuire P, Iacoponi E, Garety P, Morris E, Valmaggia L, et al. Lambeth Early Onset (LEO) and Outreach & Support in South London (OASIS) service. Early Interv Psychiatry. 2007; **1**(1): 97-103.
38. Green CE, McGuire PK, Ashworth M, Valmaggia LR. Outreach and Support in South London (OASIS). Outcomes of non-attenders to a service for people at high risk of psychosis: the case for a more assertive approach to assessment. Psychol Med. 2011; **41**(2): 243-50.
39. Kelleher I, Murtagh A, Molloy C, Roddy S, Clarke MC, Harley M, et al. Identification and characterization of prodromal risk syndromes in young adolescents in the community: a population-based clinical interview study. Schizophr Bull. 2012; **38**(2): 239-46.
40. von Reventlow HG, Kruger-Ozgurdal S, Ruhrmann S, Schultze-Lutter F, Heinz A, Patterson P, et al. Pathways to care in subjects at high risk for psychotic disorders - a European perspective. Schizophr Res. 2014; **152**(2-3): 400-7.

41. Ghali S, Fisher HL, Joyce J, Major B, Hobbs L, Soni S, et al. Ethnic variations in pathways into early intervention services for psychosis. Br J Psychiatry. 2013; **202**(4): 277-83.
42. Ciompi L. Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophr Bull. 1980; **6**(4): 606-18.
43. Helgason L. Twenty years' follow-up of first psychiatric presentation for schizophrenia: what could have been prevented? Acta Psychiatr Scand. 1990; **81**(3): 231-5.
44. Kua J, Wong KE, Kua EH, Tsoi WF. A 20-year follow-up study on schizophrenia in Singapore. Acta Psychiatr Scand. 2003; **108**(2): 118-25.
45. Kurihara T, Kato M, Reverger R, Tirta IG. Seventeen-year clinical outcome of schizophrenia in Bali. Eur Psychiatry. 2011; **26**(5): 333-8.
46. Moller HJ, Jager M, Riedel M, Obermeier M, Strauss A, Bottlender R. The Munich 15-year follow-up study (MUFUSSAD) on first-hospitalized patients with schizophrenic or affective disorders: assessing courses, types and time stability of diagnostic classification. Eur Psychiatry. 2011; **26**(4): 231-43.
47. Salokangas RK. Prognostic implications of the sex of schizophrenic patients. Br J Psychiatry. 1983; **142**: 145-51.
48. White C, Stirling J, Hopkins R, Morris J, Montague L, Tantam D, et al. Predictors of 10-year outcome of first-episode psychosis. Psychol Med. 2009; **39**(9): 1447-56.
49. van Os J, Wright P, Murray R. Follow-up studies of schizophrenia I: Natural history and non-psychopathological predictors of outcome. Eur Psychiatry. 1997; **12**(5): 83576-6.
50. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. Schizophr Bull. 1998; **24**(1): 75-85.
51. Mason P, Harrison G, Glazebrook C, Medley I, Croudace T. The course of schizophrenia over 13 years. A report from the International Study on Schizophrenia (ISoS) coordinated by the World Health Organization. Br J Psychiatry. 1996; **169**(5): 580-6.
52. Mason P, Harrison G, Glazebrook C, Medley I, Dalkin T, Croudace T. Characteristics of outcome in schizophrenia at 13 years. Br J Psychiatry. 1995; **167**(5): 596-603.
53. Harrison G, Hopper K, Craig T, Laska E, Siegel C, Wanderling J, et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. Br J Psychiatry. 2001; **178**: 506-17.
54. Malla A, Norman R, Bechard-Evans L, Schmitz N, Manchanda R, Cassidy C. Factors influencing relapse during a 2-year follow-up of first-episode psychosis in a specialized early intervention service. Psychol Med. 2008; **38**(11): 1585-93.
55. Qin H, Zhang J, Wang Z, Min H, Yan C, Chen F, et al. Duration of untreated psychosis and clinical outcomes of first-episode schizophrenia: a 4-year follow-up study. Shanghai Arch Psychiatry. 2014; **26**(1): 42-8.
56. Crumlish N, Whitty P, Clarke M, Browne S, Kamali M, Gervin M, et al. Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. Br J Psychiatry. 2009; **194**(1): 18-24.
57. Hill M, Crumlish N, Clarke M, Whitty P, Owens E, Renwick L, et al. Prospective relationship of duration of untreated psychosis to psychopathology and functional outcome over 12 years. Schizophr Res. 2012; **141**(2-3): 215-21.
58. Carbon M, Correll CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. Dialogues Clin Neurosci. 2014; **16**(4): 505-24.
59. Harrison G, Owens D, Holton A, Neilson D, Boot D. A prospective study of severe mental disorder in Afro-Caribbean patients. Psychol Med. 1988; **18**(3): 643-57.
60. Boydell J, van Os J, McKenzie K, Allardyce J, Goel R, McCreadie RG, et al. Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. Bmj. 2001; **323**(7325): 1336-8.
61. Morgan C, Dazzan P, Morgan K, Jones P, Harrison G, Leff J, et al. First episode psychosis and ethnicity: initial findings from the AESOP study. World Psychiatry. 2006; **5**(1): 40-6.

62. Davies S, Thornicroft G, Leese M, Higgingbotham A, Phelan M. Ethnic differences in risk of compulsory psychiatric admission among representative cases of psychosis in London. Bmj. 1996; **312**(7030): 533-7.
63. Harrison G, Holton A, Neilson D, Owens D, Boot D, Cooper J. Severe mental disorder in Afro-Caribbean patients: some social, demographic and service factors. Psychol Med. 1989; **19**(3): 683-96.
64. Pinto R, Ashworth M, Jones R. Schizophrenia in black Caribbeans living in the UK: an exploration of underlying causes of the high incidence rate. Br J Gen Pract. 2008; **58**(551): 429-34.
65. Morgan C, Fisher H, Hutchinson G, Kirkbride J, Craig TK, Morgan K, et al. Ethnicity, social disadvantage and psychotic-like experiences in a healthy population based sample. Acta Psychiatr Scand. 2009; **119**(3): 226-35.
66. Bhugra D, Hilwig M, Hossein B, Marceau H, Neehall J, Leff J, et al. First-contact incidence rates of schizophrenia in Trinidad and one-year follow-up. Br J Psychiatry. 1996; **169**(5): 587-92.
67. Sugarman PA, Craufurd D. Schizophrenia in the Afro-Caribbean community. Br J Psychiatry. 1994; **164**(4): 474-80.
68. Selten JP, Cantor-Graae E. The denial of a psychosis epidemic. Psychol Med. 2010; **40**(5): 731-3.
69. McGovern D, Cope R. Second generation Afro-Caribbeans and young whites with a first admission diagnosis of schizophrenia. Soc Psychiatry Psychiatr Epidemiol. 1991; **26**(2): 95-9.
70. Morgan C, Charalambides M, Hutchinson G, Murray RM. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. Schizophr Bull. 2010; **36**(4): 655-64.
71. Cooper B. Immigration and schizophrenia: the social causation hypothesis revisited: Br J Psychiatry. 2005 May;186:361-3.; 2005.
72. Goldberg EM, Morrison SL. Schizophrenia and Social Class. Br J Psychiatry. 1963; **109**: 785-802.
73. Reininghaus UA, Morgan C, Simpson J, Dazzan P, Morgan K, Doody GA, et al. Unemployment, social isolation, achievement-expectation mismatch and psychosis: findings from the AESOP Study. Soc Psychiatry Psychiatr Epidemiol. 2008; **43**(9): 743-51.
74. Morgan C, Lappin J, Heslin M, Donoghue K, Lomas B, Reininghaus U, et al. Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. Psychol Med. 2014; **44**(13): 2713-26.
75. Janssens AC, Ioannidis JP, Bedrosian S, Boffetta P, Dolan SM, Dowling N, et al. Strengthening the reporting of genetic risk prediction studies (GRIPS): explanation and elaboration. European journal of human genetics : EJHG. 2011; **19**(5): 18 p preceding 494.
76. Lieberman JA, Alvir JM, Woerner M, Degreef G, Bilder RM, Ashtari M, et al. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. Schizophr Bull. 1992; **18**(3): 351-71.
77. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000; **283**(15): 2008-12.
78. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009; **151**(4): 264-9.
79. Addington J, Addington D. Symptom remission in first episode patients. Schizophrenia Research. 2008; **106**(2-3): 281-5.
80. Alaghband-Rad J, Boroumand M, Amini H, Sharifi V, Omid A, Davari-Ashtiani R, et al. Non-affective Acute Remitting Psychosis: a preliminary report from Iran. Acta Psychiatr Scand. 2006; **113**(2): 96-101.
81. Albert N, Bertelsen M, Thorup A, Petersen L, Jeppesen P, Le Quack P, et al. Predictors of recovery from psychosis Analyses of clinical and social factors associated with recovery among patients with first-episode psychosis after 5 years. Schizophr Res. 2011; **125**(2-3): 257-66.

82. Álvarez-Jiménez M, Gleeson JF, Henry LP, Harrigan SM, Harris MG, Killackey E, et al. Road to full recovery: Longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. Psychological Medicine. 2012; **42**(3): 595-606.
83. Austin SF, Mors O, Secher RG, Hjorthøj CR, Albert N, Bertelsen M, et al. Predictors of recovery in first episode psychosis: The OPUS cohort at 10year follow-up. Schizophrenia Research. 2013; **150**(1): 163-8.
84. Benoit A, Bodnar M, Malla AK, Joober R, Bherer L, Lepage M. Changes in memory performance over a 12-month period in relation to achieving symptomatic remission after a first-episode psychosis. Schizophr Res. 2014; **153**(1-3): 103-8.
85. Berg E, Lindelius R, Petterson U, Salum I. Schizoaffective psychoses. A long-term follow-up. Acta Psychiatrica Scandinavica. 1983; **67**(6): 389-98.
86. Bernhardt S G. PROGNOSTIC CRITERIA IN HEBEPHRENIA. American Journal of Psychiatry. 1940; **97**(2): 332-41.
87. Bertelsen M, Jeppesen P, Petersen L, Thorup A, Øhlenschlæger J, Quach PL, et al. Course of illness in a sample of 265 patients with first-episode psychosis-Five-year follow-up of the Danish OPUS trial. Schizophrenia Research. 2009; **107**(2-3): 173-8.
88. Bromet EJ, Finch SJ, Carlson GA, Fochtmann L, Mojtabai R, Craig TJ, et al. Time to remission and relapse after the first hospital admission in severe bipolar disorder. Social Psychiatry and Psychiatric Epidemiology. 2005; **40**(2): 106-13.
89. Carlson GA, Bromet EJ, Sievers S. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. American Journal of Psychiatry. 2000; **157**(2): 213-9.
90. Chang WC, Tang JY, Hui CL, Lam MM, Chan SK, Wong GH, et al. Prediction of remission and recovery in young people presenting with first-episode psychosis in Hong Kong: A 3-year follow-up study. Australian and New Zealand Journal of Psychiatry. 2012; **46**(2): 100-8.
91. Chang WC, Chan TCW, Chen ESM, Hui CLM, Wong GHY, Chan SKW, et al. The concurrent and predictive validity of symptomatic remission criteria in first-episode schizophrenia. Schizophrenia Research. 2013; **143**(1): 107-15.
92. Clarke M, Whitty P, Browne S, McTigue O, Kamali M, Gervin M, et al. Untreated illness and outcome of psychosis. British Journal of Psychiatry. 2006; **189**(SEP.): 235-40.
93. Craig TJ, Bromet EJ, Fennig S, Tanenberg-Karant M, Lavelle J, Galambos N. Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? The American journal of psychiatry. 2000; **157**(1): 60-6.
94. de Haan L, Nimwegen L, Amelsvoort T, Dingemans P, Linszen D. Improvement of subjective well-being and enduring symptomatic remission, a 5-year follow-up of first episode schizophrenia. Pharmacopsychiatry. 2008; **41**(4): 125-8.
95. Emsley R, Rabinowitz J, Medori R. Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates. Schizophrenia Research. 2007; **89**(1-3): 129-39.
96. Emsley R, Oosthuizen PP, Kidd M, Koen L, Niehaus DJH, Turner HJ. Remission in first-episode psychosis: Predictor variables and symptom improvement patterns. Journal of Clinical Psychiatry. 2006; **67**(11): 1707-12.
97. Evensen J, Røssberg JI, Barder H, Haahr U, Hegelstad WTV, Joa I, et al. Flat affect and social functioning: A 10year follow-up study of first episode psychosis patients. Schizophrenia Research. 2012; **139**(1-3): 99-104.
98. Faber G, Smid HG, Van Gool AR, Wunderink L, van den Bosch RJ, Wiersma D. Continued cannabis use and outcome in first-episode psychosis: data from a randomized, open-label, controlled trial. J Clin Psychiatry. 2012; **73**(5): 632-8.
99. Fraguas D, del Rey-Mejías T, Moreno C, Castro-Fornieles J, Graell M, Otero S, et al. Duration of untreated psychosis predicts functional and clinical outcome in children and adolescents with first-episode psychosis: A 2-year longitudinal study. Schizophrenia Research. 2014; **152**(1): 130-8.

100. Gasquet I, Haro JM, Tcherny-Lessenot S, Chartier F, Lépine JP. Remission in the outpatient care of schizophrenia: 3-Year results from the Schizophrenia Outpatients Health Outcomes (SOHO) Study in France. European Psychiatry. 2008; **23**(7): 491-6.
101. Gignac A, McGirr A, Lam RW, Yatham LN. Course and outcome following a first episode of mania: Four-year prospective data from the Systematic Treatment Optimization Program (STOP-EM). Journal of Affective Disorders. 2015; **175**: 411-7.
102. Harrison G, Hopper K, Craig T, Laska E, Siegel C, Wanderling J, et al. Recovery from psychotic illness: A 15- and 25-year international follow-up study. British Journal of Psychiatry. 2001; **178**(JUNE): 506-17.
103. Harrow M, Sands JR, Silverstein ML, Goldberg JF. Course and outcome for schizophrenia versus other psychotic patients: a longitudinal study. Schizophr Bull. 1997; **23**(2): 287-303.
104. Harrow M, Grossman LS, Jobe TH, Herbener ES. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. Schizophrenia Bulletin. 2005; **31**(3): 723-34.
105. Hassan GAM, Taha GRA. Long term functioning in early onset psychosis: Two years prospective follow-up study. Behavioral and Brain Functions. 2011; **7**.
106. Hill M, Crumlish N, Clarke M, Whitty P, Owens E, Renwick L, et al. Prospective relationship of duration of untreated psychosis to psychopathology and functional outcome over 12years. Schizophrenia Research. 2012; **141**(2-3): 215-21.
107. Huber G, Gross G, Schuttler R, Linz M. Longitudinal studies of schizophrenic patients. Schizophr Bull. 1980; **6**(4): 592-605.
108. Henry LP, Amminger GP, Harris MG, Yuen HP, Harrigan SM, Prosser AL, et al. The EPPIC Follow-Up Study of First-Episode Psychosis: Longer-Term Clinical and Functional Outcome 7 Years after Index Admission. Journal of Clinical Psychiatry. 2010; **71**(6): 716-28.
109. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychological medicine Monograph supplement. 1992; **20**: 1-97.
110. Johnson S, Sathyaseelan M, Charles H, Jeyaseelan V, Jacob KS. Predictors of insight in first-episode schizophrenia: a 5-year cohort study from India. The International journal of social psychiatry. 2014; **60**(6): 566-74.
111. Jordan G, Lutgens D, Joober R, Lepage M, Iyer SN, Malla A. The relative contribution of cognition and symptomatic remission to functional outcome following treatment of a first episode of psychosis. Journal of Clinical Psychiatry. 2014; **75**(6): e566-e72.
112. Kaleda VG. The course and outcomes of episodic endogenous psychoses with juvenile onset (a follow-up study). Neuroscience and behavioral physiology. 2009; **39**(9): 873-84.
113. Kinoshita H, Nakane Y, Nakane H, Ishizaki Y, Honda S, Ohta Y, et al. Nagasaki schizophrenia study: Influence of the duration of untreated psychosis on long-term outcome. Acta Medica Nagasakiensia. 2005; **50**(1): 17-22.
114. Lambert M, Conus P, Lubman DI, Wade D, Yuen H, Moritz S, et al. The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. Acta Psychiatrica Scandinavica. 2005; **112**(2): 141-8.
115. Lambert M, Schimmelmann BG, Schacht A, Karow A, Wagner T, Wehmeier PM, et al. Long-term patterns of subjective wellbeing in schizophrenia: Cluster, predictors of cluster affiliation, and their relation to recovery criteria in 2842 patients followed over 3 years. Schizophrenia Research. 2009; **107**(2-3): 165-72.
116. Lambert M, Schimmelmann BG, Naber D, Schacht A, Karow A, Wagner T, et al. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. Journal of Clinical Psychiatry. 2006; **67**(11): 1690-7.
117. Langeveld J, Joa I, Friis S, Ten Velden Hegelstad W, Melle I, Johannessen JO, et al. A comparison of adolescent- and adult-onset first-episode, non-affective psychosis: 2-year follow-up. European Archives of Psychiatry and Clinical Neuroscience. 2012; **262**(7): 599-605.

118. Lieberman JA, Alvir JM, Koreen A, Geisler S, Chakos M, Sheitman B, et al. Psychobiologic correlates of treatment response in schizophrenia. Neuropsychopharmacology. 1996; **14**(3 SUPPL.): 13S-21S.
119. Lieberman JA, Alvir JMJ, Woerner M, Degreef G, Bilder RM, Ashtari M, et al. Prospective study of psychobiology in first-episode schizophrenia at hillside hospital. Schizophrenia Bulletin. 1992; **18**(3): 351-71.
120. Madsen AL, Vorstrup S, Rubin P, Larsen JK, Hemmingsen R. Neurological abnormalities in schizophrenic patients: A prospective follow-up study 5 years after first admission. Acta Psychiatrica Scandinavica. 1999; **100**(2): 119-25.
121. Manchanda R, Norman RMG, Malla AK, Harricharan R, Northcott S. Persistent psychoses in first episode patients. Schizophrenia Research. 2005; **80**(1): 113-6.
122. Mattsson M, Topor A, Cullberg J, Forsell Y. Association between financial strain, social network and five-year recovery from first episode psychosis. Soc Psychiatry Psychiatr Epidemiol. 2008; **43**(12): 947-52.
123. Morgan C, Lappin J, Heslin M, Donoghue K, Lomas B, Reininghaus U, et al. Reappraising the long-term course and outcome of psychotic disorders: The AESOP-10 study. Psychological Medicine. 2014; **44**(13): 2713-26.
124. Naz B, Craig TJ, Bromet EJ, Finch SJ, Fochtmann LJ, Carlson GA. Remission and relapse after the first hospital admission in psychotic depression: A 4-year naturalistic follow-up. Psychological Medicine. 2007; **37**(8): 1173-81.
125. Norman RMG, Manchanda R, Windell D. The prognostic significance of early remission of positive symptoms in first treated psychosis. Psychiatry Research. 2014; **218**(1-2): 44-7.
126. Nyman AK, Jonsson H. Differential evaluation of outcome in schizophrenia. Acta Psychiatr Scand. 1983; **68**(6): 458-75.
127. Opjordsmoen S. Long-term course and outcome in unipolar affective and schizoaffective psychoses. Acta Psychiatrica Scandinavica. 1989; **79**(4): 317-26.
128. Perkins DO, Lieberman JA, Gu H, Tohen M, McEvoy J, Green AI, et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. British Journal of Psychiatry. 2004; **185**(JULY): 18-24.
129. Rangaswamy T, Mangala R, Mohan G, Joseph J, John S. Intervention for first episode psychosis in India - The SCARF experience. Asian Journal of Psychiatry. 2012; **5**(1): 58-62.
130. Rangaswamy T, Mangala R, Mohan G, Joseph J, John S. Early intervention for first-episode psychosis in India. East Asian Archives of Psychiatry. 2012; **22**(3): 94-9.
131. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and Functional Recovery from a First Episode of Schizophrenia or Schizoaffective Disorder. American Journal of Psychiatry. 2004; **161**(3): 473-9.
132. Rund BR, Barder HE, Evensen J, Haahr U, Hegelstad WT, Joa I, et al. Neurocognition and Duration of Psychosis: A 10-year Follow-up of First-Episode Patients. Schizophr Bull. 2016; **42**(1): 87-95.
133. Salem MO, Moselhy HF, Attia H, Yousef S. Psychogenic Psychosis Revisited: A Follow up Study. International journal of health sciences. 2009; **3**(1): 45-9.
134. Schimmelmann BG, Conus P, Cotton S, Kupferschmid S, McGorry PD, Lambert M. Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. European Psychiatry. 2012; **27**(6): 463-9.
135. Shepherd M, Watt D, Falloon I, Smeeton N. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychological medicine Monograph supplement. 1989; **15**: 1-46.
136. Shrivastava A, Shah N, Johnston M, Stitt L, Thakar M. Predictors of long-term outcome of first-episode schizophrenia: A ten-year follow-up study. Indian Journal of Psychiatry. 2010; **52**(4): 320-6.

137. Simonsen E, Friis S, Opjordsmoen S, Mortensen EL, Haahr U, Melle I, et al. Early identification of non-remission in first-episode psychosis in a two-year outcome study. Acta Psychiatrica Scandinavica. 2010; **122**(5): 375-83.
138. Srivastava AK, Stitt L, Thakar M, Shah N, Chinnasamy G. The abilities of improved schizophrenia patients to work and live independently in the community: A 10-year long-term outcome study from Mumbai, India. Annals of General Psychiatry. 2009; **8**: 24.
139. Tang JYM, Chang WC, Hui CLM, Wong GHY, Chan SKW, Lee EHM, et al. Prospective relationship between duration of untreated psychosis and 13-year clinical outcome: A first-episode psychosis study. Schizophrenia Research. 2014; **153**(1-3): 1-8.
140. Thara R. Twenty-year course of schizophrenia: the Madras Longitudinal Study. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2004; **49**(8): 564-9.
141. Thorup A, Albert N, Bertelsen M, Petersen L, Jeppesen P, Le Quack P, et al. Gender differences in first-episode psychosis at 5-year follow-up--two different courses of disease? Results from the OPUS study at 5-year follow-up. European psychiatry : the journal of the Association of European Psychiatrists. 2014; **29**(1): 44-51.
142. Tohen M, Khalsa HMK, Salvatore P, Vieta E, Ravichandran C, Baldessarini RJ. Two-year outcomes in first-episode psychotic depression: The McLean-Harvard first-episode project. Journal of Affective Disorders. 2012; **136**(1-2): 1-8.
143. Tohen M, Hennen J, Zarate Jr CM, Baldessarini RJ, Strakowski SM, Stoll AL, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. American Journal of Psychiatry. 2000; **157**(2): 220-8.
144. Üçok A, Serbest S, Kandemir PE. Remission after first-episode schizophrenia: Results of a long-term follow-up. Psychiatry Research. 2011; **189**(1): 33-7.
145. Torgalsbøen AK, Mohn C, Czajkowski N, Rund BR. Relationship between neurocognition and functional recovery in first-episode schizophrenia: Results from the second year of the Oslo multi-follow-up study. Psychiatry Research. 2015; **227**(2-3): 185-91.
146. Vazquez-Barquero JL, Cuesta MJ, Herrera Castanedo S, Lastra I, Herran A, Dunn G. Cantabria first-episode schizophrenia study: three-year follow-up. The British journal of psychiatry : the journal of mental science. 1999; **174**: 141-9.
147. Verma S, Subramaniam M, Abdin E, Poon LY, Chong SA. Symptomatic and functional remission in patients with first-episode psychosis. Acta Psychiatrica Scandinavica. 2012; **126**(4): 282-9.
148. Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Substance misuse in first-episode psychosis: 15-month prospective follow-up study. The British journal of psychiatry : the journal of mental science. 2006; **189**: 229-34.
149. Whitty P, Clarke M, McTigue O, Browne S, Kamali M, Kinsella A, et al. Predictors of outcome in first-episode schizophrenia over the first 4 years of illness. Psychological Medicine. 2008; **38**(8): 1141-6.
150. Wiersma D, Wanderling J, Dragomirecka E, Ganev K, Harrison G, An Der Heiden W, et al. Social disability in schizophrenia: Its development and prediction over 15 years in incidence cohorts in six European centres. Psychological Medicine. 2000; **30**(5): 1155-67.
151. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: A 15-year followup of a Dutch incidence cohort. Schizophrenia Bulletin. 1998; **24**(1): 75-85.
152. Wunderink L, Sytema S, Nienhuis FJ, Wiersma D. Clinical recovery in first-episode psychosis. Schizophrenia Bulletin. 2009; **35**(2): 362-9.
153. Zarate CA, Jr., Tohen M, Land ML. First-episode schizophreniform disorder: comparisons with first-episode schizophrenia. Schizophr Res. 2000; **46**(1): 31-4.
154. Andreasen NC, Carpenter WT, Jr., Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry. 2005; **162**(3): 441-9.

155. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991; **48**(9): 851-5.
156. Lasser RA, Nasrallah H, Helldin L, Peuskens J, Kane J, Docherty J, et al. Remission in schizophrenia: applying recent consensus criteria to refine the concept. Schizophr Res. 2007; **96**(1-3): 223-31.
157. Lambert M, De Marinis T, Pfeil J, Naber D, Schreiner A. Establishing remission and good clinical functioning in schizophrenia: predictors of best outcome with long-term risperidone long-acting injectable treatment. Eur Psychiatry. 2010; **25**(4): 220-9.
158. Chang WC, Tang JY, Hui CL, Lam MM, Chan SK, Wong GH, et al. Prediction of remission and recovery in young people presenting with first-episode psychosis in Hong Kong: a 3-year follow-up study. Aust N Z J Psychiatry. 2012; **46**(2): 100-8.
159. Larsen TK, Melle I, Auestad B, Haahr U, Joa I, Johannessen JO, et al. Early detection of psychosis: positive effects on 5-year outcome. Psychol Med. 2011; **41**(7): 1461-9.
160. Modestin J, Huber A, Satirli E, Malti T, Hell D. Long-term course of schizophrenic illness: Bleuler's study reconsidered. Am J Psychiatry. 2003; **160**(12): 2202-8.
161. Harrow M, Grossman LS, Jobe TH, Herbener ES. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. Schizophr Bull. 2005; **31**(3): 723-34.
162. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 2004; **161**(3): 473-9.
163. Addington DE, McKenzie E, Wang J. Validity of Hospital Admission as an Outcome Measure of Services for First-Episode Psychosis. Psychiatric Services. 2012; **63**(3): 280-2.
164. Bland RC, Orn H. 14-year outcome in early schizophrenia. Acta Psychiatr Scand. 1978; **58**(4): 327-38.
165. Ceskova E, Prikryl R, Kasparek T. Outcome in males with first-episode schizophrenia: 7-year follow-up. World Journal of Biological Psychiatry. 2011; **12**(1): 66-72.
166. Cullberg J, Mattsson M, Levander S, Holmqvist R, Tomsmark L, Elingfors C, et al. Treatment costs and clinical outcome for first episode schizophrenia patients: a 3-year follow-up of the Swedish "Parachute Project" and two comparison groups. Acta Psychiatr Scand. 2006; **114**(4): 274-81.
167. DeLisi LE, Stritzke P, Riordan H, Holan V, Boccio A, Kushner M, et al. The timing of brain morphological changes in schizophrenia and their relationship to clinical outcome. Biological psychiatry. 1992; **31**(3): 241-54.
168. Geddes J, Mercer G, Frith CD, MacMillan F, Owens DG, Johnstone EC. Prediction of outcome following a first episode of schizophrenia. A follow-up study of Northwick Park first episode study subjects. The British journal of psychiatry : the journal of mental science. 1994; **165**(5): 664-8.
169. Henisz J. A follow-up study of schizophrenic patients. Comprehensive Psychiatry. 1966; **7**(6): 524-8.
170. Ho BC, Nopoulos P, Flaum M, Arndt S, Andreasen NC. Two-year outcome in first-episode schizophrenia: predictive value of symptoms for quality of life. The American journal of psychiatry. 1998; **155**(9): 1196-201.
171. Jabs BE, Krause U, Althaus G, Bartsch AJ, Stöber G, Pfuhlmann B. Differences in quality of life and course of illness between cycloid and schizophrenic psychoses - A comparative study. World Journal of Biological Psychiatry. 2004; **5**(3): 136-42.
172. Johnstone EC, Macmillan JF, Frith CD, Benn DK, Crow TJ. Further investigation of the predictors of outcome following first schizophrenic episodes. The British journal of psychiatry : the journal of mental science. 1990; **157**: 182-9.
173. Kam SM, Singh SP, Upthegrove R. What needs to follow early intervention? Predictors of relapse and functional recovery following first-episode psychosis. Early Interv Psychiatry. 2015; **9**(4): 279-83.

174. McCreadie RG, Wiles D, Grant S, Crockett GT, Mahmood Z, Livingston MG, et al. The Scottish first episode schizophrenia study. VII. Two-year follow-up. Scottish Schizophrenia Research Group. Acta Psychiatr Scand. 1989; **80**(6): 597-602.
175. Moller HJ, Bottlender R, Gross A, Hoff P, Wittmann J, Wegner U, et al. The Kraepelinian dichotomy: preliminary results of a 15-year follow-up study on functional psychoses: focus on negative symptoms. Schizophr Res. 2002; **56**(1-2): 87-94.
176. Munk-Jørgensen P, Mortensen PB. Social outcome in schizophrenia: a 13-year follow-up. Social Psychiatry and Psychiatric Epidemiology. 1992; **27**(3): 129-34.
177. Racenstein JM, Harrow M, Reed R, Martin E, Herbener E, Penn DL. The relationship between positive symptoms and instrumental work functioning in schizophrenia: a 10 year follow-up study. Schizophr Res. 2002; **56**(1-2): 95-103.
178. Salokangas RKR. Living situation and social network in schizophrenia. A prospective 5-year follow-up study. Nordic Journal of Psychiatry. 1996; **50**(1): 35-42.
179. Sarotar BN, Pesek MB, Agius M, Kocmur M. Duration of untreated psychosis and it's effect on the symptomatic recovery in schizophrenia - Preliminary results. Neuroendocrinology Letters. 2008; **29**(6): 990-4.
180. Shrivastava A, Johnston M, Thakar M, Stitt L, Shah N. Social outcome in clinically recovered first-episode schizophrenia in a naturalistic, ten-year, follow-up study in India. Clinical Schizophrenia and Related Psychoses. 2011; **5**(2): 95-101.
181. Sim K, Chan YH, Chong SA, Siris SG. A 24-month prospective outcome study of first-episode schizophrenia and schizoaffective disorder within an early psychosis intervention program. J Clin Psychiatry. 2007; **68**(9): 1368-76.
182. Singh SP, Croudace T, Amin S, Kwiecinski R, Medley I, Jones PB, et al. Three-year outcome of first-episode psychoses in an established community psychiatric service. British Journal of Psychiatry. 2000; **176**(MAR.): 210-6.
183. Soskis DA, Harrow M, Detre TP. Long-term follow-up of schizophrenics admitted to a general hospital psychiatric ward. The Psychiatric Quarterly. 1969; **43**(1-4): 525-34.
184. Stirling J, White C, Lewis S, Hopkins R, Tantam D, Huddy A, et al. Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. Schizophr Res. 2003; **65**(2-3): 75-86.
185. Takei N, Persaud R, Woodruff P, Brockington I, Murray RM. First episodes of psychosis in Afro-Caribbean and White people. An 18-year follow-up population-based study. Br J Psychiatry. 1998; **172**: 147-53.
186. Turner MA, Boden JM, Smith-Hamel C, Mulder RT. Outcomes for 236 patients from a 2-year early intervention in psychosis service. Acta Psychiatrica Scandinavica. 2009; **120**(2): 129-37.
187. Wieselgren IM, Lindstrom LH. A prospective 1-5 year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment. Acta Psychiatr Scand. 1996; **93**(1): 9-19.
188. Zhang-Wong J, Beiser M, Bean G, Iacono WG. Five-year course of schizophreniform disorder. Psychiatry Res. 1995; **59**(1-2): 109-17.
189. Schennach-Wolff R, Jager M, Seemuller F, Obermeier M, Messer T, Laux G, et al. Defining and predicting functional outcome in schizophrenia and schizophrenia spectrum disorders. Schizophr Res. 2009; **113**(2-3): 210-7.
190. Kane JM. Factors which can make patients difficult to treat. Br J Psychiatry Suppl. 1996; **31**: 10-4.
191. Meltzer HY. Treatment-resistant schizophrenia--the role of clozapine. Curr Med Res Opin. 1997; **14**(1): 1-20.
192. NICE. Psychosis and schizophrenia in adults: treatment and management (Clinical guideline 178). London: Royal College of Psychiatrists; 2014.

193. Selten JP, Hoek HW. Does misdiagnosis explain the schizophrenia epidemic among immigrants from developing countries to Western Europe?: Soc Psychiatry Psychiatr Epidemiol. 2008 Dec;43(12):937-9. doi: 10.1007/s00127-008-0390-5.
194. Harrison G, Ineichen B, Smith J, Morgan HG. Psychiatric hospital admissions in Bristol. II. Social and clinical aspects of compulsory admission. Br J Psychiatry. 1984; **145**: 605-11.
195. Leese M, Thornicroft G, Shaw J, Thomas S, Mohan R, Harty MA, et al. Ethnic differences among patients in high-security psychiatric hospitals in England. Br J Psychiatry. 2006; **188**: 380-5.
196. Mohan R, McCrone P, Szmukler G, Micali N, Afuwape S, Thornicroft G. Ethnic differences in mental health service use among patients with psychotic disorders. Soc Psychiatry Psychiatr Epidemiol. 2006; **41**(10): 771-6.
197. Birchwood M, Cochrane R, Macmillan F, Copestake S, Kucharska J, Carriss M. The influence of ethnicity and family structure on relapse in first-episode schizophrenia. A comparison of Asian, Afro-Caribbean, and white patients. Br J Psychiatry. 1992; **161**: 783-90.
198. McKenzie K, Samele C, Van Horn E, Tattan T, Van Os J, Murray R. Comparison of the outcome and treatment of psychosis in people of Caribbean origin living in the UK and British Whites. Report from the UK700 trial. Br J Psychiatry. 2001; **178**: 160-5.
199. McGovern D, Hemmings P, Cope R, Lowerson A. Long-term follow-up of young Afro-Caribbean Britons and white Britons with a first admission diagnosis of schizophrenia. Soc Psychiatry Psychiatr Epidemiol. 1994; **29**(1): 8-19.
200. Larsen TK, Melle I, Auestad B, Friis S, Haahr U, Johannessen JO, et al. Early detection of first-episode psychosis: the effect on 1-year outcome. Schizophr Bull. 2006; **32**(4): 758-64.
201. Gafoor R, Nitsch D, McCrone P, Craig TK, Garety PA, Power P, et al. Effect of early intervention on 5-year outcome in non-affective psychosis. Br J Psychiatry. 2010; **196**(5): 372-6.
202. Norman RM, Manchanda R, Windell D, Harricharan R, Northcott S, Hassall L. The role of treatment delay in predicting 5-year outcomes in an early intervention program. Psychol Med. 2012; **42**(2): 223-33.
203. Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 1999; **56**(3): 241-7.
204. Hegelstad WT, Larsen TK, Auestad B, Evensen J, Haahr U, Joa I, et al. Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. Am J Psychiatry. 2012; **169**(4): 374-80.
205. Thara R, Henrietta M, Joseph A, Rajkumar S, Eaton WW. Ten-year course of schizophrenia--the Madras longitudinal study. Acta Psychiatr Scand. 1994; **90**(5): 329-36.
206. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl. 1998; **172**(33): 53-9.
207. Wheeler A, Humberstone V, Robinson G. Outcomes for schizophrenia patients with clozapine treatment: how good does it get? J Psychopharmacol. 2009; **23**(8): 957-65.
208. Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull. 2006; **32**(4): 715-23.
209. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Comparative Effectiveness of Clozapine and Standard Antipsychotic Treatment in Adults With Schizophrenia. American Journal of Psychiatry. 2015; **0**(0): appi.ajp.2015.15030332.
210. Schennach R, Riedel M, Musil R, Moller HJ. Treatment Response in First-episode Schizophrenia. Clin Psychopharmacol Neurosci. 2012; **10**(2): 78-87.
211. Ortiz BB, Araujo Filho GM, Araripe Neto AG, Medeiros D, Bressan RA. Is disorganized schizophrenia a predictor of treatment resistance? Evidence from an observational study. Rev Bras Psiquiatr. 2013; **35**(4): 432-4.
212. Vanelle JM, Olie JP, Levy-Soussan P. New antipsychotics in schizophrenia: the French experience. Acta psychiatrica Scandinavica Supplementum. 1994; **380**: 59-63.

213. Lin CC, Wang YC, Chen JY, Liou YJ, Bai YM, Lai IC, et al. Artificial neural network prediction of clozapine response with combined pharmacogenetic and clinical data. Computer methods and programs in biomedicine. 2008; **91**(2): 91-9.
214. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry. 2012; **201**(6): 481-5.
215. Ten Velden Hegelstad W, Haahr U, Larsen TK, Auestad B, Barder H, Evensen J, et al. Early detection, early symptom progression and symptomatic remission after ten years in a first episode of psychosis study. Schizophr Res. 2013; **143**(2-3): 337-43.
216. Marchesi C, Affaticati A, Monici A, De Panfilis C, Ossola P, Tonna M. Predictors of symptomatic remission in patients with first-episode schizophrenia: a 16years follow-up study. Compr Psychiatry. 2014; **55**(4): 778-84.
217. Malla A, Norman R, Schmitz N, Manchanda R, Bechard-Evans L, Takhar J, et al. Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. Psychol Med. 2006; **36**(5): 649-58.
218. Allardyce J, McCreadie RG, Morrison G, van Os J. Do symptom dimensions or categorical diagnoses best discriminate between known risk factors for psychosis? Soc Psychiatry Psychiatr Epidemiol. 2007; **42**(6): 429-37.
219. Demjaha A, Morgan K, Morgan C, Landau S, Dean K, Reichenberg A, et al. Combining dimensional and categorical representation of psychosis: the way forward for DSM-V and ICD-11? Psychol Med. 2009; **39**(12): 1943-55.
220. Bakker PR, Wichers M, van Harten PN, Myin-Germeys I, Delespaul P, van Os J. Novel directions for psychiatric diagnosis: from psychopathology to motor function to monitoring technology. Epidemiol Psychiatr Sci. 2013; **22**(4): 289-95.
221. Stewart R, Soremekun M, Perera G, Broadbent M, Callard F, Denis M, et al. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry. 2009; **9**(51): 9-51.
222. Perera G, Broadbent M, Callard F, Chang CK, Downs J, Dutta R, et al. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. BMJ Open. 2016; **6**(3): 2015-008721.
223. Mallett R, Leff J, Bhugra D, Pang D, Zhao JH. Social environment, ethnicity and schizophrenia. A case-control study. Soc Psychiatry Psychiatr Epidemiol. 2002; **37**(7): 329-35.
224. Norman RM, Malla AK. Duration of untreated psychosis: a critical examination of the concept and its importance. Psychol Med. 2001; **31**(3): 381-400.
225. Compton MT, Chien VH, Leiner AS, Goulding SM, Weiss PS. Mode of onset of psychosis and family involvement in help-seeking as determinants of duration of untreated psychosis. Soc Psychiatry Psychiatr Epidemiol. 2008; **43**(12): 975-82.
226. Morgan C, Abdul-Al R, Lappin JM, Jones P, Fearon P, Leese M, et al. Clinical and social determinants of duration of untreated psychosis in the AESOP first-episode psychosis study. Br J Psychiatry. 2006; **189**: 446-52.
227. Greenland S. Interactions in epidemiology: relevance, identification, and estimation. Epidemiology. 2009; **20**(1): 14-7.
228. WHO. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva. 1992.
229. Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry. 2015; **2**(3): 233-8.
230. Morgan C, Mallett R, Hutchinson G, Bagalkote H, Morgan K, Fearon P, et al. Pathways to care and ethnicity. 1: Sample characteristics and compulsory admission. Report from the AESOP study. Br J Psychiatry. 2005; **186**: 281-9.

231. Babor TF, J. R. de la Fuente, et al. . "The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Health Care". In: Geneva SWHOP, editor.; 1989.
232. Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, et al. High-potency cannabis and the risk of psychosis. Br J Psychiatry. 2009; **195**(6): 488-91.
233. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system: Arch Gen Psychiatry. 48(8):764-70.; 1991.
234. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987; **13**(2): 261-76.
235. Singh SP, Cooper JE, Fisher HL, Tarrant CJ, Lloyd T, Banjo J, et al. Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS). Schizophr Res. 2005; **80**(1): 117-30.
236. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry. 1976; **33**(6): 766-71.
237. Burns T, Creed F, Fahy T, Thompson S, Tyrer P, White I. Intensive versus standard case management for severe psychotic illness: a randomised trial. UK 700 Group. Lancet. 1999; **353**(9171): 2185-9.
238. Sartorius N, Gulbinat W, Harrison G, Laska E, Siegel C. Long-term follow-up of schizophrenia in 16 countries. A description of the International Study of Schizophrenia conducted by the World Health Organization. Soc Psychiatry Psychiatr Epidemiol. 1996; **31**(5): 249-58.
239. Susser E, Finnerty M, Mojtabai R, Yale S, Conover S, Goetz R, et al. Reliability of the life chart schedule for assessment of the long-term course of schizophrenia. Schizophr Res. 2000; **42**(1): 67-77.
240. Revier CJ, Reininghaus U, Dutta R, Fearon P, Murray RM, Doody GA, et al. Ten-Year Outcomes of First-Episode Psychoses in the MRC AESOP-10 Study. The Journal of nervous and mental disease. 2015; **203**(5): 379-86.
241. Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry. 1992; **149**(9): 1183-8.
242. Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr Bull. 2014; **40**(2): 314-26.
243. Stefanovics EA, Elkis H, Zhening L, Zhang XY, Rosenheck RA. A cross-national factor analytic comparison of three models of PANSS symptoms in schizophrenia. Psychiatry Res. 2014; **219**(2): 283-9.
244. Valmaggia LR, Byrne M, Day F, Broome MR, Johns L, Howes O, et al. Duration of untreated psychosis and need for admission in patients who engage with mental health services in the prodromal phase. Br J Psychiatry. 2015; **207**(2): 130-4.
245. Tanskanen S, Morant N, Hinton M, Lloyd-Evans B, Crosby M, Killaspy H, et al. Service user and carer experiences of seeking help for a first episode of psychosis: a UK qualitative study. BMC Psychiatry. 2011; **11**(157): 11-157.
246. Shrivastava A. Should "risk syndrome for psychosis" be included as a diagnosis in DSM-V? World Psychiatry. 2010; **9**(2): 123.
247. Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry. 2001; **50**(11): 884-97.
248. Morgan C, Mallett R, Hutchinson G, Bagalkote H, Morgan K, Fearon P, et al. Pathways to care and ethnicity. 2: Source of referral and help-seeking. Report from the AESOP study. Br J Psychiatry. 2005; **186**: 290-6.
249. Bechard-Evans L, Schmitz N, Abadi S, Joober R, King S, Malla A. Determinants of help-seeking and system related components of delay in the treatment of first-episode psychosis. Schizophr Res. 2007; **96**(1-3): 206-14.
250. Alvidrez J, Snowden LR, Kaiser DM. The experience of stigma among Black mental health consumers. J Health Care Poor Underserved. 2008; **19**(3): 874-93.

251. Platz C, Umbricht DS, Cattapan-Ludewig K, Dvorsky D, Arbach D, Brenner HD, et al. Help-seeking pathways in early psychosis. Soc Psychiatry Psychiatr Epidemiol. 2006; **41**(12): 967-74.
252. Bentall R. Madness explained: why we must reject the Kraepelinian paradigm and replace it with a 'complaint-orientated' approach to understanding mental illness. Med Hypotheses. 2006; **66**(2): 220-33.
253. Sastry N. A nested frailty model for survival data, with an application to the study of child survival in northeast Brazil. J Am Stat Assoc. 1997; **92**(438): 426-35.
254. Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med. 2006; **144**(9): 650-9.
255. Elderd BD, Dwyer G, Dukic V. Population-level differences in disease transmission: a Bayesian analysis of multiple smallpox epidemics. Epidemics. 2013; **5**(3): 146-56.
256. Marchesi C, Affaticati A, Monici A, De Panfilis C, Ossola P, Tonna M. Severity of core symptoms in first episode schizophrenia and long-term remission. Psychiatry Res. 2015; **225**(1-2): 129-32.
257. Mirowsky J, 2nd, Ross CE. Minority status, ethnic culture, and distress: a comparison of Blacks, Whites, Mexicans, and Mexican Americans. Ajs. 1980; **86**(3): 479-95.
258. Harrow M, Grossman LS, Herbener ES, Davies EW. Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders and mood-incongruent psychotic symptoms. Br J Psychiatry. 2000; **177**: 421-6.
259. Jaaskelainen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013; **39**(6): 1296-306.
260. Dazzan P. Neuroimaging biomarkers to predict treatment response in schizophrenia: the end of 30 years of solitude? Dialogues Clin Neurosci. 2014; **16**(4): 491-503.
261. White L, Harvey PD, Opler L, Lindenmayer JP. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. Psychopathology. 1997; **30**(5): 263-74.
262. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. Five-factor model of schizophrenia. Initial validation. J Nerv Ment Dis. 1994; **182**(11): 631-8.
263. Schwartz JE, Fennig S, Tanenberg-Karant M, Carlson G, Craig T, Galambos N, et al. Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. Arch Gen Psychiatry. 2000; **57**(6): 593-600.
264. McGorry P, Johanessen JO, Lewis S, Birchwood M, Malla A, Nordentoft M, et al. Early intervention in psychosis: keeping faith with evidence-based health care. Psychol Med. 2010; **40**(3): 399-404.
265. Craig TKJ, Garety P, Power P, Rahaman N, Colbert S, Fornells-Ambrojo M, et al. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. BMJ. 2004; **329**(7474): 1067.
266. Zipursky RB, Reilly JL, Murray RM. The myth of schizophrenia as a progressive brain disease. Schizophr Bull; 2012.
267. Albus M. Clinical courses of schizophrenia. Pharmacopsychiatry. 2012; **45**(1): 0032-1308968.
268. Tulloch AD, Fearon P, David AS. Timing, prevalence, determinants and outcomes of homelessness among patients admitted to acute psychiatric wards. Soc Psychiatry Psychiatr Epidemiol. 2012; **47**(7): 1181-91.
269. Mann F, Fisher HL, Major B, Lawrence J, Tapfumaneyi A, Joyce J, et al. Ethnic variations in compulsory detention and hospital admission for psychosis across four UK Early Intervention Services. BMC Psychiatry. 2014; **14**(1): 256.
270. Compton MT. Barriers to initial outpatient treatment engagement following first hospitalization for a first episode of nonaffective psychosis: a descriptive case series. J Psychiatr Pract. 2005; **11**(1): 62-9.

271. McGovern D, Hemmings P. A follow-up of second generation Afro-Caribbeans and white British with a first admission diagnosis of schizophrenia: attitudes to mental illness and psychiatric services of patients and relatives. Soc Sci Med. 1994; **38**(1): 117-27.
272. Perkins RE, Moodley P. Perception of problems in psychiatric inpatients: denial, race and service usage. Soc Psychiatry Psychiatr Epidemiol. 1993; **28**(4): 189-93.
273. Sundermann O, Onwumere J, Kane F, Morgan C, Kuipers E. Social networks and support in first-episode psychosis: exploring the role of loneliness and anxiety. Soc Psychiatry Psychiatr Epidemiol. 2014; **49**(3): 359-66.
274. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines: World Health Organization; 1992.
275. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med. 2002; **21**(16): 2409-19.
276. van Os J, Wright P, Murray RM. Follow-up studies of schizophrenia I: Natural history and non-psychopathological predictors of outcome. European Psychiatry. 1997; **12, Supplement 5**: 327s-41s.
277. Vanelle JM. [Treatment refractory schizophrenia]. Encephale. 1995; **21 Spec No 3**: 13-21.
278. Meltzer HY, Rabinowitz J, Lee MA, Cola PA, Ranjan R, Findling RL, et al. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. Am J Psychiatry. 1997; **154**(4): 475-82.
279. Wimberley T, Pedersen CB, MacCabe JH, Stovring H, Astrup A, Sorensen HJ, et al. Inverse association between urbanicity and treatment resistance in schizophrenia. Schizophr Res. 2016; **174**(1-3): 150-5.
280. Frank J, Lang M, Witt SH, Strohmaier J, Rujescu D, Cichon S, et al. Identification of increased genetic risk scores for schizophrenia in treatment-resistant patients: Mol Psychiatry. 2015 Feb;20(2):150-1. doi: 10.1038/mp.2014.56. Epub 2014 Jun 3.
281. Hettige NC, Cole CB, Khalid S, De Luca V. Polygenic risk score prediction of antipsychotic dosage in schizophrenia. Schizophr Res. 2016; **170**(2-3): 265-70.
282. Ikeda M, Yoshimura R, Hashimoto R, Kondo K, Saito T, Shimasaki A, et al. Genetic overlap between antipsychotic response and susceptibility to schizophrenia: J Clin Psychopharmacol. 2015 Feb;35(1):85-8. doi: 10.1097/JCP.0000000000000268.
283. Huber CG, Naber D, Lambert M. Incomplete remission and treatment resistance in first-episode psychosis: definition, prevalence and predictors. Expert Opin Pharmacother. 2008; **9**(12): 2027-38.
284. Demjaha A LJ, Patel MX, Morgan K, MacCabe J, Howes OD, Heslin M, Reininghaus U, Donoghue K, Lomas B, Charalambides M, Onyejiaka A, Fearon P, Jones PB, Doody G, Murray RM, Morgan C, Dazzan P. Resistance to antipsychotic drug treatment from the illness onset: Findings from the 10-year follow up of the AESOP first episode psychosis study. . (in submission). 2015; **Personal communication**.
285. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, et al. Antipsychotic Treatment Resistance in Schizophrenia Associated with Elevated Glutamate Levels but Normal Dopamine Function. Biological Psychiatry. 2014; **75**(5): e11-e3.
286. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry. 2012; **169**(11): 1203-10.
287. McCutcheon R, Beck K, Bloomfield MA, Marques TR, Rogdaki M, Howes OD. Treatment resistant or resistant to treatment? Antipsychotic plasma levels in patients with poorly controlled psychotic symptoms. J Psychopharmacol. 2015; **29**(8): 892-7.
288. Broussard B, Kelley ME, Wan CR, Cristofaro SL, Crisafio A, Haggard PJ, et al. Demographic, socio-environmental, and substance-related predictors of duration of untreated psychosis (DUP). Schizophr Res. 2013; **148**(1-3): 93-8.
289. Susser E, Fennig S, Jandorf L, Amador X, Bromet E. Epidemiology, diagnosis, and course of brief psychoses. Am J Psychiatry. 1995; **152**(12): 1743-8.

290. Crespo-Facorro B, Roiz-Santianez R, Pelayo-Teran JM, Gonzalez-Blanch C, Perez-Iglesias R, Gutierrez A, et al. Caudate nucleus volume and its clinical and cognitive correlations in first episode schizophrenia. Schizophr Res. 2007; **91**(1-3): 87-96.
291. Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 1999; **156**(4): 544-9.
292. Kolakowska T, Williams AO, Ardern M, Reveley MA, Jambor K, Gelder MG, et al. Schizophrenia with good and poor outcome. I: Early clinical features, response to neuroleptics and signs of organic dysfunction. Br J Psychiatry. 1985; **146**: 229-39.
293. Iyo M, Tadokoro S, Kanahara N, Hashimoto T, Niitsu T, Watanabe H, et al. Optimal extent of dopamine D2 receptor occupancy by antipsychotics for treatment of dopamine supersensitivity psychosis and late-onset psychosis. J Clin Psychopharmacol. 2013; **33**(3): 398-404.
294. Chouinard G. Severe cases of neuroleptic-induced supersensitivity psychosis. Diagnostic criteria for the disorder and its treatment. Schizophr Res. 1991; **5**(1): 21-33.
295. Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. J Clin Psychiatry. 2011; **72**(11): 1439-44.
296. Nielsen J, Nielsen RE, Correll CU. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. J Clin Psychopharmacol. 2012; **32**(5): 678-83.
297. Ucok A, Cikrikcili U, Karabulut S, Salaj A, Ozturk M, Tabak O, et al. Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2015; **30**(5): 290-5.
298. Beck K, McCutcheon R, Bloomfield MA, Gaughran F, Reis Marques T, MacCabe J, et al. The practical management of refractory schizophrenia--the Maudsley Treatment REview and Assessment Team service approach. Acta Psychiatr Scand. 2014; **130**(6): 427-38.
299. Wade D, Harrigan S, Harris MG, Edwards J, McGorry PD. Pattern and correlates of inpatient admission during the initial acute phase of first-episode psychosis. Australian and New Zealand Journal of Psychiatry. 2006; **40**(5): 429-36.
300. Bhopal R. Is research into ethnicity and health racist, unsound, or important science? Bmj. 1997; **314**(7096): 1751-6.
301. Cannon TD, Yu C, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, et al. An Individualized Risk Calculator for Research in Prodromal Psychosis. Am J Psychiatry. 2016; **173**(10): 980-8.
302. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003; **60**(12): 1187-92.
303. Gottesman, II, Shields J. A polygenic theory of schizophrenia. Proc Natl Acad Sci U S A. 1967; **58**(1): 199-205.
304. Walton E, Turner J, Gollub RL, Manoach DS, Yendiki A, Ho BC, et al. Cumulative genetic risk and prefrontal activity in patients with schizophrenia. Schizophr Bull. 2013; **39**(3): 703-11.
305. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009; **460**(7256): 748-52.
306. Consortium SWGotPG. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; **511**(7510): 421-7.
307. McIntosh AM, Gow A, Luciano M, Davies G, Liewald DC, Harris SE, et al. Polygenic risk for schizophrenia is associated with cognitive change between childhood and old age. Biol Psychiatry. 2013; **73**(10): 938-43.
308. van Scheltinga AF, Bakker SC, van Haren NE, Derks EM, Buizer-Voskamp JE, Cahn W, et al. Schizophrenia genetic variants are not associated with intelligence. Psychol Med. 2013; **15**: 1-8.

309. Lencz T, Knowles E, Davies G, Guha S, Liewald DC, Starr JM, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). Mol Psychiatry. 2014; **19**(2): 168-74.
310. Derks EM, Vorstman JA, Ripke S, Kahn RS, Ophoff RA. Investigation of the genetic association between quantitative measures of psychosis and schizophrenia: a polygenic risk score analysis. PLoS One. 2012; **7**(6): 22.
311. Fanous AH, Zhou B, Aggen SH, Bergen SE, Amdur RL, Duan J, et al. Genome-wide association study of clinical dimensions of schizophrenia: polygenic effect on disorganized symptoms. Am J Psychiatry. 2012; **169**(12): 1309-17.
312. Tesli M, Espeseth T, Bettella F, Mattingsdal M, Aas M, Melle I, et al. Polygenic risk score and the psychosis continuum model. Acta Psychiatr Scand. 2014; **25**(10): 12307.
313. Sieradzka D, Power RA, Freeman D, Cardno AG, McGuire P, Plomin R, et al. Are genetic risk factors for psychosis also associated with dimension-specific psychotic experiences in adolescence? PLoS One. 2014; **9**(4).
314. Iniesta R, Malki K, Maier W, Rietschel M, Mors O, Hauser J, et al. Combining clinical variables to optimize prediction of antidepressant treatment outcomes. J Psychiatr Res. 2016; **78**: 94-102.

Subject number: 2EU02. |__|__|__|__|

Date of Birth |__|__|-|_|_|-|**1**|**9**|__|_ |

Date |__|__|-|_|_|-|**2**|**0**|__|_ |

Social (1) Socio-demographics (at first contact)

1. Gender **[**O -77 Not Recorded] O1 Male O2 Female

2. Age **[**O -77 Not Recorded] |__|__|

3. Postcode **[**O -77 Not Recorded] |__|__|__|__|-|__|__|__|__|

4. Ethnicity **[**O -77 Not Recorded]

O11White British	O12 White Irish	O13 White gypsy, traveller	O14 Other White
O15 Mixed (w, bc)	O16 Mixed (w, ba)	O17 Mixed (w, as)	O18 Other Mixed
O19 Indian	O20 Pakistani	O21 Bangladeshi	O22 Chinese
O23 Other Asian	O24 Black Caribbean	O25 Black African	O26 Other Black
O27 Arab	O28 Other, specify: _____		

5. Place of Birth **[**O -77 Not Recorded]

O1 Austria	O2 Belgium	O3 France	O4 Germany
O5 Ireland	O6 Italy	O7 Spain	O8 Suisse
O9 The Netherlands	O10 Turkey	O11 United Kingdom	O12 Brazil
O13 Australia	O14 other, specify: _____		

6. Age of migration (if applicable) **[**O -77 Not Recorded] |__|__|

7. Ever employed (paid work) **[**O -77 Not Recorded] O0 No
O1 Yes

8. Registered with a GP **[**O -77 Not Recorded] O0 No
O1 Yes

9. Lives with

Alone	Alone, with children	Partner, Spouse	Partner, Spouse, with children	Parents	Other family	Friends	Other: specify (e.g. hostel, halls of residence)	Not Recorded
O1	O2	O3	O4	O5	O6	O7	O8_____	O -77

10. Housing tenure

Privately owned (self)	Privately owned (family)	Rented (Private)	Rented (government)	Other, specify:	Not Recorded
O1	O2	O3	O4	O5_____	O -77

11. Ever had a long-term relationship (one year or more) **[**O -77 Not Recorded] O0 No
O1 Yes

12. Number of children ...? **[**O -77 Not Recorded]
|__|__|

13. Relationship status …?

Single	Married, living with someone	In a steady relationship	Divorced, separated	Widowed	Not Recorded
O1	O2	O3	O4	O5	O -77

14. Highest level of education achieved ...? **[**O -77 Not Recorded]

O1	School, no qualifications	(to end of compulsory education; passed no exams, tests, etc.)
O2	School, with qualifications	(to end of compulsory education; passed one or more exams, tests, etc.)
O3	Tertiary, Further	(first level of non-compulsory education; e.g. A-levels, Baccalaureate)
O4	Vocational	(job related education, e.g. teacher training, plumber, electrician, etc.)
O5	Higher (undergraduate)	(University; first degree)
O6	Higher (postgraduate)	(University: higher than first degree level, e.g. Masters, PhD)

15. Employment status …?

Unemployed	Economically inactive (i.e. house person, physical illness/disability, career, retired)	Student	Part-time employee	Full-time employee	Self-employed	Not Recorded
O1	O2	O3	O4	O5	O6	O -77

16. Weekly + contact with family **[**O -77 Not Recorded] O0 No
O1 Yes

17. Weekly + contact with friends **[**O -77 Not Recorded] O0 No
O1 Yes

18. Any report of socially isolation **[**O -77 Not Recorded] O0 No
O1 Yes

DUP

Please note the most accurate date!

- In case only information about the *year of onset* is available, please note the 1st of July of that year as date of onset
- In case only information about the *month of onset* is available, please note the 15th of that month as date of onset

Date of onset psychosis:

First day of onset of psychotic symptoms

Onset of psychotic symptoms is defined as: Clear evidence of delusions, hallucinations, first rank symptoms, catatonic symptoms (i.e. A score of 2 for a psychotic symptom in Part II of the SCAN OR a score ≥ 4 on PANSS items P1, 'delusions', P3 'hallucinatory behaviour', P5 'Grandiosity', P6 'Suspiciousness' or A9 'Unusual thought content').

Date of contact with mental health services (for FEP)

(day/month/year): **[**O -77 Not Recorded] ☐☐ – ☐☐ – ☐☐☐☐

Date of onset psychosis: **[**O -77 Not Recorded] ☐☐ ☐☐ ☐☐☐☐

Mode of Onset

O1 Abrupt onset definable to within hours or days

O2 Acute onset definable to within 1 week

O3 Moderately acute onset definable within 1 month

O4 Gradual onset over period up to 6 months

O5 Insidious onset over period greater than 6 months

Pathway to Care

1 Mode of Contact (Secondary Mental Health Service) ☐ 0 = Community; 1 = Home treatment; 2 = In-patient (voluntary); 3 = In-patient (compulsory); -77 = Not recorded

2 MHA Section (if applicable) ☐

1 = Section 2 | 6 = Section 37 | -77 = Not recorded
2 = Section 3 | 7 = Section 37/41
3 = Section 4 | 8 = Section 47
4 = Section 5(2) | 9 = Section 48
5 = Section 5(4)

2a. MHA Sec 136/135 ☐ 0= No 1= Yes -77= Not recorded

3 Source of Referral ☐ 1 = General practitioner; 2 = Nurse, other health worker, or social worker;
3 = Accident and Emergency; 4 = Police; 5 = Courts; 6 = Prison;
7 = Other, specify; -77 = Not recorded

4 Contact out of hours ☐ 0 = No 1 = Yes -77 = Not recorded

5 Family Involvement ☐ 0 = No 1 = Yes -77 = Not recorded

6 Police or CJA Involvement ☐ 0 = No 1 = Yes -77 = Not recorded

Family History

[O -77 Not Recorded]

1. Evidence of history of mental illness in first degree relative? O0 No O1 Probable O2 Definite

If probable or definite, complete following for each affected relative:

No.	Relative (1 Father; 2 Mother; 3 Sibling; 4 Child)	Age	Treatment (1 GP; 2 Social worker; 3 Other)	Treatment setting (1 Inpatient; 2 Outpatient; 3 Medication only)	Reliability of information (1 Good; 2 Fair; 3 Poor)	Type of Disorder
1.						
2.						
3.						
4.						
5.						

Substance Use

1 Ever smoked/used cannabis? [O -77 Not Recorded] O1 Yes O0 No

Global Assessment of Functioning (GAF) Scale - SYMPTOMS

Subject number: _____

Rating: _____

Consider psychological functioning on a hypothetical continuum of mental health-illness.

Rate symptoms over the last week before interview. Use intermediate codes where appropriate e.g. 45, 68, 72.

100-91	**No symptoms.**
90-81	**Absent or minimal symptoms** (e.g. mild anxiety before an exam).
80-71	**If symptoms are present they are transient and expectable reactions to psychosocial stresses** (e.g. difficulty concentrating after family argument).
70-61	**Some mild symptoms** (e.g. depressed mood and mild insomnia).
60-51	**Moderate symptoms** (e.g. flat affect and circumstantial speech, occasional panic attacks).
50-41	**Serious symptoms** (e.g. suicide ideation, severe obsessional rituals, frequent shoplifting)**.**
40-31	**Some impairment in reality testing or communication** (e.g. speech is at times illogical, obscure or irrelevant).
30-21	**Behaviour is considered influenced by delusions or hallucinations OR serious impairment in communications or judgment** (e.g. sometimes incoherent, acts grossly inappropriately, suicidal preoccupation).
20-11	**Some danger or hurting self or others** (e.g. suicide attempts without clear expectation of death, frequently violent, manic excitement) **OR gross impairment in communication** (e.g. largely incoherent or mute).
10-1	**Persistent danger of severely hurting self or others** (e.g. recurrent violence) **serious suicidal act with clear expectation of death.**

Global Assessment of Functioning (GAF) Scale - DISABILITY

Subject number: _____

Rating: _____

Consider psychological, social and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment of function due to physical or environmental limitations.
Rate functioning over the last week before interview. Use intermediate codes where appropriate e.g. 45, 68, 72.

100-91	**Superior functioning in a wide range of activities; life's problems never get out of hand; is sought out by others because of his/her positive qualities.**
90-81	**Good functioning in all areas, interested and involved in a wide range or activities, socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g. an occasional argument with family members).
80-71	**No more than slight impairment in social, occupational, or school functioning** (e.g. temporarily falling behind in school work).
70-61	**Some difficulty in social, occupational, or school functioning (e.g. occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.**
60-51	**Moderate difficulty in social, occupational, or school functioning** (e.g. few friends, conflicts with co-workers).
50-41	**Any serious impairment in social, occupational, or school functioning** (e.g. no friends, unable to keep a job).
40-31	**Major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood** (e.g. depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).
30-21	**Inability to function in almost all areas** (e.g. stays in bed all day; no job, home or friends).
20-11	**Occasionally fails to maintain minimal personal hygiene (e.g. smears faeces) OR gross impairment in communication** (e.g. largely incoherent or mute).
10-1	**Persistent inability to maintain minimum personal hygiene.**

[DATE]

[GP PRACTICE]
[ADDRESS]
[City Postcode[

Dear [GP PRACTICE],

Re: [First Name] [Second Name] [DOB]

I am writing to you with regard to the above patient, who to my knowledge, is currently on your caseload. This patient participated in a study on First-Episode Psychosis, the Genetics and Psychosis (GAP) Study in our centre-Institute of Psychiatry, King's College London-and agreed that he could be followed-up (Ethics reference number: 05/Q0706/158; the patient consent form is attached).

We are now trying to contact all those who participated in the study. Unfortunately, we have been unable to get in touch with the patient. We think that this may be due to change in the patient's contact details since our previous contact. We would be very grateful if you were able to provide us with the relevant contact information, i.e. current mobile phone number and/or home number of patient. This would allow us to re-assess a larger cohort of patients with a pre-existing psychotic disorder and would be of immense benefit for the scientific and clinical community.

Although we do realise that you must be very busy with your clinical commitments, we would really appreciate if you could respond to the questions I have enclosed to this letter and either fax this form back to me on Fax: 020 7848 0287 or by post in the envelop provided.

Should you have further queries, please contact my colleague Olesya Ajnakina on 020 7848 0518. Thank you in advance for your cooperation.

Yours sincerely,

Professor Robin M Murray
MD DSc FRCP FRCPsych FMedSci FRS
Professor of Psychiatric Research

Short Questionnaire for GPs: First-Episode Psychosis, the Genetics and Psychosis (GAP)
Name/DOB/First contact

Is the above patient still in contact with you? **Y/N**

If yes, when was the last time the patient was seen by any member of the surgery staff?

……../……../……

Current the patient's contact details:
Home address:
……..……...……
……...……
…….....…

Phone number (or other means of contact):
……...……
…….....

Currently, is the patient under the care of the local Community Mental Health Team (CMHT)? **Y/N**

If Yes, since when the patient has been under the care of the local CMHT:

…….....…/……./…….

Would it be possible to provide the contact details of the patient's current CMHT?.....
.....
.....
.....

What medication the patient's she currently on?
.....

Are you aware of the presence of suicidal behaviour, i.e. the patient required medical attention (A&E or hospitalization) following a deliberate self-harm act? If so, could you please prove the details?
.....
.....
.....
.....
.....

Has the patient ever been admitted to hospital with mental health issues since the patient has been on your caseload? **Y/N**

Please provide us with some details

……
……
……
……

Additional comments:

Is there anything that we should take into consideration when we contact with patients?.....
.....
.....
.....
.....
.....

Name of the Participant: ……..
ID: ……
Date of birth: ……
Date of the assessment: ……. .
Name of the Assessor:……
Date of First Contact: ……

SECTION 1: **CLINICAL COURSE AND SYMPTOMS**

NOTE: COMLETE **TIME LINE SHEET,** PLOTTING EACH PSYCHOTIC EPISODE

2.1 CURRENT MENTAL STATE

Is the patient now (last 30 days) in a psychotic episode? ☐

0 = No

1 = Yes

2 = Yes, but not continuous with episode in inclusion

If impossible to assess, specify reason

2.2 REMISSION

a) What is longest period (in weeks) during which the patient has had a remission of psychotic symptoms?
(Use definition of remission in Appendix 1, without the 6 month requirement) ☐

b) Has the patient had a remission of psychotic symptoms for a period of at least **6 months** since the initial evaluation?
(See Appendix 1 for definition of remission)

☐

0 = No 1 = Yes

If impossible to assess, specify reason

b) If YES above, for how many weeks was the patient in the episode of inclusion (i.e. baseline episode)
(888 = patient still in episode of inclusion) ☐

2.3 USUAL SYMPTOM SEVERITY (during psychotic episodes only)

☐

0 = No further episodes

1 = Mild

2 = Moderate

3 = Severe

Note: Use SCAN rating criteria

'The severity of a symptom can be assessed in terms of duration, persistence, degree of interference with other mental functions, distress, impairment of everyday activities, effect on other people, and contact with services of various kinds.'

SCAN Rating Scales

0 Symptom(s) did not occur during period

1 Symptom(s) definitely occurred during period, but probably uncommon or transitory
OR of such a minor degree it is not appropriate for use in classification

2 Symptom(s) definitely present, on multiple occasions or for part of time, during period
AND at a level sufficient to use in classification

3 Symptom was more or less continuously present throughout the period/episode AND present in severe form

2.4 PRESENCE OF NEGATIVE SYMPTOMS

(Over follow-up period)

0 = No
1 = Yes, for less than 6 months
2 = Yes, for more than 6 months

i.e.
a) Marked reduction or loss of interests, initiative and drive, leading to serious deterioration of the performance of usual activities and tasks
b) Emergence or marked exacerbation of social withdrawal (active avoidance of communication with other people)
c) Gross and persistent self-neglect

2.5. COURSE TYPE

1 = **Episodic**, no episode lasted over 6 months
2 = **Continuous**, no remission lasted over 6 months (Primarily symptoms A)
3 = **Continuous**, no remission lasted over 6 months (Primarily symptoms B)
4 = **Continuous**, no remission lasted over 6 months (Primarily symptoms A & B)
5 = **Neither episodic nor continuous**, at least 1 episode & 1 remission lasted over 6 months

IF EPISODIC OR NEITHER EPISODIC NOR CONTINUOUS, RATE ITEM 2.6. – 2.7.
IF NEVER PSYCHOTIC OR CONTINUOUS GO TO ITEM 2.6.

2.6. NUMBER OF PSYCHOTIC EPISODES (Do NOT include first episode)

(See Appendix 1 for definition of psychotic episode. Each "psychotic episode" must be separated by at least **6 months** spent in remission).

0.0 = Patient presently in remission from episode of inclusion

2.7 MONTHS OF LONGEST PSYCHOTIC EPISODE

2.8 SUICIDE ATTEMPT(S)

a) Rate the number of suicide attempts by the patient since the index episode of evaluation (if in any doubt re: intention, rate as deliberate self-harm)
0 = None

2.9 DELIBERATE SELF-HARM

a) Rate the number of episodes of deliberate self-harm by the patient since the index episode of evaluation (if in any doubt re: intention, rate as deliberate self-harm)
0 = None
b) Record details of suicide attempts and episodes of deliberate self-harm

SECTION 2: **SERVICE USE AND TREATMENT**

3.1 HAS THE PATIENT BEEN IN CONTACT WITH SERVICES AT ANY POINT DURING THE FOLLOW-UP PERIOD?

0 = No
1 = Yes

If YES, continue
If NO, is this because:

0 = None were offered
1 = Patient did not attend

If 1, specify reasons for this:

……
……
……

3.1a. TOTAL NUMBER OF HOSPITAL ADMISSIONS

3.1.b. TOTAL NUMBER OF PERIODS OF COMMUNITY TREATMENT

Note: ALL RECORDED CONTACTS MUST BE FOR ANY MENTAL ILLNESS. NOTE WHETHER CONTACT WAS FOR PSYCHOSIS OR NEUROSIS ON TIME LINE SHEET.

NOTE: COMPLETE TIME LINE SHEET, PLOTTING EACH HOSPITAL ADMISSION, EACH PERIOD OF COMMUNITY TREATMENT AND EACH PERIOD OF NON-CONTACT

HOSPITAL ADMISSIONS (1)

3.2 COMPLETE FOR EACH HOSPITAL ADMISSIONS DURING THE FOLLOW-UP PERIOD (inc. first admission), USING CODES PROVIDED BELOW
(use further sheets if necessary)

3.2.1 Date of Admission ……/……/……..

3.2.2 Date of Discharge ……/……/……..

3.2.3 Ward Type ☐

3.2.4a MHA Status on Admission ☐

3.2.4.b MHA Status during Admission ☐

3.2.5. MHA Section(s)
(Specify section from the list below) ☐

3.2.6 Source of Referral ☐

3.2.7 Reason for Admission
(nb: there can be more than 1 reason
for admission) ☐

3.2.8. Family Involvement ☐

3.2.9. Police or CJA Involvement ☐

Comments (add further relevant details)**:**
……
……
……

CODES FOR HOSPITAL ADMISSIONS

3.2.3 Ward type

What type of ward was the patient admitted to?

0 = Acute

1 = Rehabilitation

2 = Secure/Forensic

3 = Other, specify

3.2.4 MHA Status

What was the mode of admission?

0 = Voluntary

1 = Compulsory

3.2.5. MHA Section (s)

Section of Mental Health Act used, if applicable

1-Section 2

2=Section 3

3=Section 4

4=Section 5(2)

5=Section 5(4)

6=Section 37

7=Section 37/41

8=Section 47

9=Section 48

10-Section 136

3.2.6 Source of Referral

What was the source of referral resulting in hospital admission?

1 = Psychiatrist or other mental health professional

2 = General practitioner

3 = Nurse, other health worker, or social worker

4 = Accident and Emergency

5 = Emergency Clinic

6 = Police

7 = Courts/Prison

8 = Other, specify

3.2.7 Reason for Admission

What were the main reasons for admission?

0 = Patient attempted suicide or bodily harm

1 = Patient's behaviour perceived as potential danger to himself (e.g., talked of killing or harming himself; refusal of food, etc.).

2 = Patient committed an assault, or other violent or hazardous act (e.g., setting fire or destroying property)

3 = Patient's behaviour perceived by others as threatening or grossly annoying.

4 = Deterioration in mental health

5 = Other reason (specify)

3.2.8. Family involvement

Were the patient's family or friends involved in seeking help that resulted in hospital; admission?

0=No

1=Yes

3.2.9. Police or CJA Involvement

Were the police or any other criminal justice agency involved in bringing about hospital admission?

0=No

1=Yes

USE OF OUTPATIENT/COMMUNITY SERVICE (1)

3.3 COMPLETE FOR EACH PERIOD OF CONTACT WITH OUTPATIENT/COMMUNITY SERVICES DURING THE FOLLOW-UP PERIOD (inc. first contact), USING CODES PROVIDED BELOW (use further sheets if necessary)

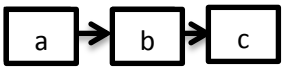
3.3.1. Date of Referral

3.3.2.a Date Last Seen

3.3.2.b Date of Discharge or Hospital admission

3.3.3. Source of Referral

3.3.4. Type of Contact
(Specify details below for all changes in type of contact)



3.3.5. Reason Contact Ended

Comments (add further relevant details)**:**
……
……
……

Please add all other relevant details (inc. any changes in type of contact, etc.)

CODES FOR USE OF OUTPATIENT/COMMUNITY SERVICES

3.3.3. Source of Referral

What was the source of referral resulting in contact with community/follow-up services?

1=Psychiatric referral following discharge from hospital
2=General practitioner
3=Nurse, other health worker, or social worker
4=Accident and Emergency
5=Emergency clinic
6=Police
7=Courts/Prison
8=Other specify

3.3.4. Type of Contact

Rate type of contact with community/follow-up services

0=Maintenance [Contact with services, inc. GP, at intervals of more than one month primary for prescription/monitoring of medication]
1=Regular [Contact with services at interval of less than one month]
2=Intensive [Contact with assertive outreach services]
3=Acute [Contact with acute home treatment/crisis intervention services]

3.3.5. Reason Contact Ended

Why was contact with community/follow-up services ended?

0=Patient was discharged by service
1=Patient was (re)admitted to hospital
2=Patient did not attend follow-up appointments

OTHER TREATMENT ITEMS

3.4.1. Overall Compliance/Attendance

EPJS ☐

Rate patient's compliance/attendance at community/follow-up services

1 = Regular compliance/attendance [1-33% missed appointments]
2 = Irregular compliance/attendance [34-66% missed appointments]
3 = None compliance/attendance [67-100% missed appointments]

3.4.2. Reason for Irregular or None Attendance

What was the reason(s) why the patient did not fully attend follow-up appointments?

……
……
……
……

EPJS ☐

3.4.3. Current treatment status

Patient's treatment status at the time of interview

0 = Not in any form of treatment
1 = Inpatient psychiatric facility (includes general hospital psychiatric wards)
2 = Standard outpatient/CMHT
3 = Assertive outreach
4 = Acute home treatment/crisis intervention
5 = Other, specify
6 = More than one above, specify

3.4.4. Traditional treatment

A great variety of traditional healing practices exists and the particular form applied should be described in a narrative

0=No
1=Yes ☐
9=Uncertain

Give detail below:

……
……
……
……

SECTION 3: **ANTI-PSYCHOTIC TREATMENT OVER FOLLOW-UP PERIOD**

1. **Name of antipsychotic**: **……**

Dose and delivery method: **……/……**

Date of commencement: **……/……/……**

Date of treatment discontinuation: **……/……/……....**

Time on treatment (weeks): ☐

Reason for discontinuation:

[1= change to alternative antipsychotic; 2= discontinued by treating physician; 3=discontinued by patient; 4= discontinued by treating physician due to side effects; 5= discontinued by treating physician due lack of therapeutic effects; 6=other] ☐

Adherence to antipsychotic over this period:
[1 (0-33%) ; 2 (33-67%) ; 3 (67-100%)] ☐

---

2. **Name of antipsychotic**: **……**

Dose and delivery method: **……/……**

Date of commencement: **……/……/……**

Date of treatment discontinuation: **……/……/……....**

Time on treatment (weeks): ☐

Reason for discontinuation:

[1= change to alternative antipsychotic; 2= discontinued by treating physician; 3=discontinued by patient; 4= discontinued by treating physician due to side effects; 5= discontinued by treating physician due lack of therapeutic effects; 6=other] ☐

Adherence to antipsychotic over this period:
[1 (0-33%) ; 2 (33-67%) ; 3 (67-100%)] ☐

---

3. **Name of antipsychotic:** **……**

Dose and delivery method: **……/……**

Date of commencement: **……/……/……**

Date of treatment discontinuation: **……/……/……....**

Time on treatment (weeks): ☐

Reason for discontinuation:

[1= change to alternative antipsychotic; 2= discontinued by treating physician; ☐
3=discontinued by patient; 4= discontinued by treating physician due to side effects; 5= discontinued by treating physician due lack of therapeutic effects; 6=other]

Adherence to antipsychotic over this period: ☐
[1 (0-33%) ; 2 (33-67%) ; 3 (67-100%)]

---

4. **Name of antipsychotic:** ……

Dose and delivery method: ……/……

Date of commencement: ……/……/……

Date of treatment discontinuation: ……/……/……....

Time on treatment (weeks): ☐

Reason for discontinuation:

[1= change to alternative antipsychotic; 2= discontinued by treating physician; ☐
3=discontinued by patient; 4= discontinued by treating physician due to side effects; 5= discontinued by treating physician due lack of therapeutic effects; 6=other]

Adherence to antipsychotic over this period: ☐
[1 (0-33%) ; 2 (33-67%) ; 3 (67-100%)]

---

5. **Name of antipsychotic:** ……

Dose and delivery method: ……/……

Date of commencement: ……/……/……

Date of treatment discontinuation: ……/……/……....
Time on treatment (weeks): ☐

Reason for discontinuation:

[1= change to alternative antipsychotic; 2= discontinued by treating physician; ☐
3=discontinued by patient; 4= discontinued by treating physician due to side effects; 5= discontinued by treating physician due lack of therapeutic effects; 6=other]

Adherence to antipsychotic over this period: ☐
[1 (0-33%) ; 2 (33-67%) ; 3 (67-100%)]

SECTION 4: **SOCIODEMOGRAPHIC SCHEDULE**

5.1. Living arrangements

00 = Living alone (excludes supervised accommodation)
01 = Living alone with children (single parent)
02 = Living with partner
03 = Living with other family
04 = Living with friends
05 = Living with unrelated persons (exclude supervised accommodations)
06 = Living in supervised accommodations (e.g. hospital, hostel, half-way house, etc.)
07 = Patient is homeless and has no stable living arrangements
99 = No information/not known/impossible to assess

5.2. How many people do live with you?

5.3. Approximate length of residence(rate to nearest week)

88=Pateint a vagrant with no stable household

5.4. Type of accommodation at follow-up?

0 = Self/joint owner occupied
1 = Family owner occupied
2 = Private rented
3 = Local Authority rented
4 = Housing Association rented
5 = Other (specify)

5.5. Current Marital Status

Rate the patient's current marital status
0 = Married or common law marriage
1 = In steady relationship
2 = Single, no partner
3 = Divorced
4 = Separated
5 = Widowed
6 = Other, specify

5.6. Main Marital Status during follow up period

Rate the patient's current marital status
0 = Married or common law marriage
1 = In steady relationship
2 = Single, no partner
3 = Divorced
4 = Separated
5 = Widowed
6 = Other, specify

5.7.Current Parental Status

Rate patient's current parental status
0 = No children

1 = Parent, living with partner
2 = Single parent
3 = Parent, children live with other parent
4 = Parent, children live with relatives
5 = Parent, children in care

5.8. Past Parental Status

Rate patient's parental status during majority of follow-up period

0 = No children
1 = Parent, living with partner
2 = Single parent
3 = Parent, children live with other parent
4 = Parent, children live with relatives
5 = Parent, children in care

5.9. Current Employment Status (LAST 30 days)

Has the patient been employed at a paid job (i.e., an earning occupation) in the last 30 days?

0=No
1=Yes
2=Student

5.10. Reason for the current unemployment (LAST 30 DAYS)

If the patient has not had a paid job in the last 30 days, rate the reasons for unemployment

0 = Related to the patient's mental illness (inc.'s hospitalisation, simple refusal to work, etc.)
1 = Unrelated to the patient's mental illness
2 = Other, specify
3 = Combination of the above, specify

5.11. Past Employment

Rate employment (or earning job) since indec episode (exclude last 30 days)

0=Has been employed 75-100% of the time
1=Has been employed 50-75% of the time
2=Has been employed 25-50% of the time
3-Has been employed 0-25% of the time

5.12. REASONS FOR PAST UNEMPLOYMENT

Rate reason for unemployment since index episode (exclude last 30 days)

0 = Related to the patient's mental illness (inc.'s hospitalisation, simple refusal to work, etc.)
1 = Unrelated to the patient's mental illness
2 = Other, specify
3 = Combination of the above, specify

5.13. EDUCATION: Since the index episode has the patient undertaken an educational programme (including vocational training), of at least 10 weeks duration?

0 = No
1 = Yes

5.14. MONTHS IN PRISON DURING FOLLOW-UP PERIOD

5.15. ANY OTHER SUGGESTIONS OF ANTI-SOCIAL/OFFENDING BEHAVIOUR?

0 = No 1 = Yes

SOCIAL NETWORK: CHANGES

5.16. HAS THE PATIENT'S RELATIONSHIP WITH FAMILY/FRIENDS BEEN AFFECTED BY HIS/HER ILLNESS?

(NB: Friends here refers only to very close friends the patient had at baseline)

1 = Yes

2 = No

5.17. IF YES, HOW

1 = Increased frequency of contact

2 = Decreased frequency of contact

5.18. FOR EITHER OF THE ABOVE, DETERMINE THE DEGREE OF CHANGE

1 = To a large extent (e.g. change from low to high frequency or vice versa)

2 = To a moderate extent (e.g. change from medium to high frequency or vice versa)

3 = To a small extent (e.g. change from low to medium frequency or vice versa)

ENSURE THAT THE CHANGE IS FROM THE PRE-MORBID FUNCTIONING LEVEL.
Check the definitions of frequency of contact below

5.19. IF THE PATIENT SEES LESS OF ANY FAMILY MEMBER(S)/FRIEND(S), WHY IS THIS?

0 = Because of illness

1 = Family quarrels

2 = Moved away

3 = Drifted apart

4 = Died

5 = Other, specify

SOCIAL NETWORK: CURRENT

5.20. HOW OFTEN DO YOU VISIT OR SPEAK TO FAMILY/FRIEND(S)?

0 = Daily

1 = Weekly

2 = Fortnightly

3 = Monthly

4 = < than above

5 = Never

5.21. DO YOU HAVE ANY CLOSE CONFIDANTS?

1 = Yes 2 = No

5.22. HOW OFTEN DO YOU VISIT/SPEAK TO CONFIDANTS?

0 = Daily

1 = Weekly

2 = Fortnightly

3 = Monthly

4 = < than above

5 = Never

SECTION 5: **DRUG ABUSE/DEPENDENCE**

a) Rate illicit drug taking and/or abuse of illicit drugs over life course ☐

0= None

1= Sporadic drug taking or occasional abuses reported, no evidence for frequent or regular use (i.e. less than one month)

2= Sporadic drug taking or occasional abuses reported, but there is reason to suspect frequent or regular use (i.e. more than one month)

3= Frequent or regular use definitely present (i.e. more than one month)

4= Substance abuse (Maladaptive use leading to any of the following (1) failure to fulfil major role obligations due to substance (2) substance exacerbating or leading to social or interpersonal problems (3) recurrent abuse when physically hazardous (e.g. driving) or substance related legal problems)

5= Substance dependence (Maladaptive use leading to 3 of the following (1) increased tolerance (2) symptoms of withdrawal (3) substance taken in larger amounts over a longer period than originally intended (4) persistent desire or unsuccessful attempts to cut down (5) much time spent in activities to obtain the substance or recovering from effects (6) impairment of social, occupational or recreational activities due to substance (7) persistent use despite harmful physical or psychological effects of substance.

7= Drug taking a definite possibility but impossible to assess the frequency and extent of use

b) If a rating of 1, 2, 3, 4,5 or 7 was made above, specify whatever information is available about the nature of the substance(s) taken by the patient. For each substance used, specify age of first use.

0 = No 1 = Yes

2 = Suspected/uncertain 8 = Not applicable/not inquired

9 = No information/impossible to assess

	Age 1st Used		Follow Up	
Morphine or heroin	_____	.....		
Opium	_____	.....		
Amphetamines or derivatives	_____	.....		
Hashish or marijuana	_____	.....		
Hallucinogens (LSD and others)	_____	.....		
Cocaine and cocopaste	_____	.....		
Barbituates	_____	.....		
Non-barbiturate sedatives and tranquillisers	_____	.....		
Other, specify	_____	.....		

c) if a rating of 4 or 5 was made date periods of substance abuse or dependence

Period 1_____

Period 2_____

Period 3_____

Period 4_____

SECTION 6: **ALCOHOL ABUSE/DEPENDENCE**

a) Rate the patient's drinking habits over life course

0= Does not drink at all
1 = Only occasional social drinking (mean 10 units or less per week)
2 = Moderate alcohol use (mean 21 units or less per week)
3 = Excessive alcohol use (mean more than 21 unit per week regularly)
4 = Alcohol abuse (Maladaptive use leading to any of the following (1) failure to fulfil major role obligations due to alcohol (2) substance exacerbating or leading to social or interpersonal problems (3) recurrent abuse when physically hazardous (e.g. driving) or alcohol related legal problems)
5 = Alcohol dependence (Maladaptive use leading to 3 of the following (1) increased tolerance (2) symptoms of withdrawal (3) alcohol taken in larger amounts over a longer period than originally intended (4) persistent desire or unsuccessful attempts to cut down (5) much time spent drinking the substance or recovering from effects (6) impairment of social, occupational or recreational activities due to alcohol (7) persistent use despite harmful physical or psychological effects of alcohol
9 = No information/Not known

b) If a rating of 3, 4, 5 or 7 was made above, specify whatever information is available about the nature of the substance(s) taken by the patient

c) if a rating of 4 or 5 was made date periods of alcohol abuse or dependence

Period 1_____
Period 2_____
Period 3_____
Period 4_____

LIST OF PAPERS RESULTED FROM THIS THESIS

John Lally,* Olesya Ajnakina,* Brendon Stubbs, Michael Cullinane, Kieran Murphy, Fiona Gaughran, Robin M Murray (under review). Remission and recovery from first-episode psychosis in adults: A systematic review and meta-analysis of long term outcome studies. *American Journal of Psychiatry*.

Olesya Ajnakina*, John Lally*, Marta Di Forti, Anna Kolliakou, Poonam Gardner-Sood, Javier Lopez-Morinigo, Paola Dazzan, Carmine Pariante, Valeria Mondelli, James MacCabe, Anthony David, Fiona Gaughran, Craig Morgan, Robin Murray, Evangelos Vassos (under review). Patterns of illness and care over the 5 years following onset of psychosis in different ethnic groups. *Social Psychiatry and Psychiatric Epidemiology*

Lally J*, Ajnakina O*, Di Forti M, Trotta A, Demjaha A, Kolliakou A, Mondelli V, Reis Marques T, Pariante C, Dazzan P, Shergil SS, Howes OD, David AS, MacCabe JH, Gaughran F, Murray RM. (2016) Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychological Medicine* 8, 1-10

*Both are first named authors and should be acknowledged as such